NRG ONCOLOGY
NSABP PROTOCOL B-47

ClinicalTrials.gov NCT01275677

A Randomized Phase III Trial of Adjuvant Therapy Comparing Chemotherapy Alone (Six Cycles of Docetaxel Plus Cyclophosphamide or Four Cycles of Doxorubicin Plus Cyclophosphamide Followed by Weekly Paclitaxel) to Chemotherapy Plus Trastuzumab in Women with Node-Positive or High-Risk Node-Negative HER2-Low Invasive Breast Cancer

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations (U.S. Institutions): the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG

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Protocol B-47 IND #113988 (trastuzumab), sponsored by the NCI

STUDY DRUG	NSC#	DRUG SUPPLY
Trastuzumab	688097	Genentech, a Member of the Roche Group, through the NCI and through F. Hoffmann-La Roche, Ltd. for ICORG

NCI Version Date: February 8, 2018 (Replaces all other versions)

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Document History

	Version/Update Date	**Broadcast Date**
Amendment 8	February 8, 2018	-
Amendment 7	May 26, 2016	June 30, 2016
Amendment 6	November 28, 2014	June 15, 2015
Amendment 5	April 16, 2014	July 2, 2014
Amendment 4	April 2, 2013	May 20, 2013
Amendment 3	March 12, 2013	May 20, 2013
Update 1	January 3, 2012	January 26, 2012
Amendment 2	December 12, 2011	January 26, 2012
Amendment 1	September 15, 2011	January 26, 2012
Activation	November 5, 2010	January 6, 2011

PROTOCOL REVISION RECORD

Original Version: November 5, 2010

Amendment #1: September 15, 2011

Sections Changed/Added:

Cover Page
Information Resources
CTSU Information Resources
Glossary of Selected Abbreviations and Acronyms
Section 1.0: Schema
Section 4.0: 4.2.6, 4.2.7, 4.3.1, 4.3.13
Section 5.0: 5.1 (Table 6)
Section 6.0: 6.0 (Tables 8, 9, 10)
Section 7.0: 7.1 (Table 11)
Section 8.0: 8.2.1
Section 9.0: 9.3 (Table 15), 9.4 (Table 16)
Section 12: 12.2
Section 13.0: 13.3.4 (Table 31), 13.3.5 (Table 32), 13.3.6, 13.6
Appendix E: 1.0, 4.0, 5.1, 6.1
Appendix F: Inserted new appendix; subsequent appendix has been relettered
Appendix G: Pages 13, 15, 17

Amendment #2: December 13, 2011

Sections Changed:

Information Resources
Section 6.0: 6.0 (Table 8 and Table 9)
Section 13.0: 13.1.1, 13.2 (Table 30), 13.4.2, 13.5
Appendix F: Paragraph 1, 2.0, 3.0
Appendix G: Pages 10, 11

Update #1: January 3, 2012

Sections Changed:

Cover Page
Section 12.0: 12.2
Appendix G: Cover Page, Page 1

Amendment #3: March 12, 2013

Sections Changed:

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Information resources
Section 4.0: 4.2.6
Section 6.0: (Table 9)
Section 8.0: 8.2.6.1, 8.3.5.1
Section 9.0: 9.3 (Table 16)
Section 11.0: 11.1
Section 12.0: 12.2, 12.2.2, 12.2.6, 12.2.7, 12.2.8
Section 13.0: 13.3
Section 18.0: 18.0
Appendix E 1.0

Amendment #4: April 2, 2013

Sections Changed:

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Section 12.0: 12.2, 12.2.2, 12.2.6, 12.2.7, 12.2.8
Section 18.0: 18.0
Appendix E 1.0

Amendment #5: April 16, 2014

Sections Changed:

Throughout the protocol, the following have been changed:

- *The NSABP and the NSABP Operations Center were changed to NRG Oncology where appropriate.*
- *All references to NSABP Biostatistical Center have been changed to NRG Oncology Statistics and Data Management Center (SDMC).*
- *Division has been changed to Department throughout the protocol where appropriate.*
- *References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)."*

Cover Page
Information Resources
CTSU Information Resources
Glossary of Selected Abbreviations and Acronyms
Section 13.0: 13.1.1, 13.2 (Table 30), 13.3, new 13.3.7 added and subsequent sections renumbered, 13.3.8
Section 15.0: New Sections 15.1, 15.2, and 15.3 added and subsequent sections renumbered, 15.5, 15.8
Section 16.0: 16.2, 16.3
Appendix E: Deleted and subsequent appendix relettered
Sample Consent Form

Amendment #6: November 28, 2014

Sections Changed:

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Amendment #7: May 26, 2016

Sections Changed:

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Section 3.0: 3.2.6
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Section 12.0: 12.2
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Amendment #8: February 8, 2018

Sections Changed:

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INFORMATION RESOURCES

NRG Oncology http://www.nsabp.pitt.edu		
NRG Oncology	Nova Tower 2 Two Allegheny Center – Suite 1200 Pittsburgh, PA 15212	Phone: 412-339-5300
NRG Oncology Statistics and Data Management Center (SDMC)	One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213	Phone: 412-624-2666 Fax: 412-624-1082 (General office fax)
Questions/problems regarding IRB review & informed consent	NRG Oncology Department of Regulatory Affairs	Phone: 412-339-5300 E-mail: regulatory@nsabp.org
Submission of IRB approval	CTSU Regulatory Office 1818 Market Street, Suite 3000 Philadelphia, PA 19103	Regulatory Submission Portal: (Sign in at www.ctsu.org)
Questions concerning eligibility and clinical aspects of the trial	NRG Oncology Clinical Coordinating Department	Phone: 1-800-477-7227 E-mail: ccdpgh@nrgoncology.org
Questions concerning drug orders, shipments, transfers, and returns (see Section 12.0)	NRG Oncology SDMC	Phone: 412-624-2666 Fax: 412-624-1082
	For mail (USPS): Pharmaceutical Management Branch, CTEP, DCTD NCI Shady Grove Room 5W228, MSC 9725 9609 Medical Center Drive Bethesda, MD 20892-9725 ***For express courier:*** Pharmaceutical Management Branch, CTEP, DCTD NCI Shady Grove Room 5W228, MSC 9725 9609 Medical Center Drive Rockville, MD 20850	Phone: 240-276-6575 Fax: 240-276-7893 E-mail: PMBAfterHours@mail.nih.gov
Submission of tumor blocks (see Section 7.0)	NRG Oncology SDMC One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213 ***Note: when sending blocks, or other materials, please indicate on the package "Pathology Specimens Enclosed."***	*Questions regarding receipt of specimens:* Phone: 412-624-2666 *For all other questions:* Phone: 412-697-6611 *Refer to the B-47 Pathology and Correlative Science Instructions in the Members' Area of the NSABP Web site or the CTSU Member Web site.*
Arrangement for return of blocks that are not to be stored or to request kits for 2 mm core sampling of existing tumor/lymph node block(s)	NRG Oncology Biospecimen Bank-Pittsburgh	E-mail: nrgbiobankpgh@nrgoncology.org Phone: 412-697-6611
Submission of all blood samples	Baylor College of Medicine NRG Oncology Serum Bank Room N1220 One Baylor Plaza Houston, TX 77030	Phone: 713-798-1647 Fax: 713-798-1642 *Refer to the B-47 Pathology and Correlative Science Instructions in the Members' Area of the NSABP Web site or the CTSU Member Web site.*

INFORMATION RESOURCES (continued)

Questions concerning expedited adverse event reporting (see Section 13.3)	NRG Oncology SDMC B-47 AE Reporting Nurse	Phone: 412-383-2557 Fax: 412-622-2113 SAEReportingpgh@nrgoncology.org
Submission of patient-completed questionnaires (see Section 8.3)	NRG Oncology SDMC B-47 Data Manager	Phone: 412-624-2666 Fax: 412-622-2115 *Refer to the B-47 Data Forms page in the Members' Area of the NSABP Web site or the CTSU Member Web site.*
Submission of data forms/questions concerning data management	NRG Oncology SDMC B-47 Data Manager	Phone: 412-624-2666 *Refer to the B-47 Data Forms page in the Members' Area of the NSABP Web site or the CTSU Member Web site.*

CANCER TRIALS SUPPORT UNIT (CTSU) INFORMATION RESOURCES

<table>
<tr>
<td>For regulatory requirements:
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.

Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td>
<td>For patient enrollments:

Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</td>
<td>Submit study data directly to the NRG Oncology SDMC through the Online Data Entry function unless otherwise specified in the protocol.
Submit study data online through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. Contact the Support Desk at support@nrgoncology.org for an account.

NRG Oncology Statistics and Data Management Center
One Sterling Plaza
201 North Craig Street, Suite 500
Pittsburgh, PA 15213

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
<tr>
<td colspan="3">• For clinical questions (i.e. patient eligibility or treatment-related), contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227.
• For data submission questions, contact the B-47 Data Manager at NRG Oncology SDMC by calling 412-624-2666.</td>
</tr>
<tr>
<td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or data submission)</u>, contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td>
</tr>
<tr>
<td colspan="3">The CTSU Member Web site is located at https://www.ctsu.org</td>
</tr>
<tr>
<td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td>
</tr>
</table>

GLOSSARY OF SELECTED ABBREVIATIONS AND ACRONYMS

AC	doxorubicin (Adriamycin) and cyclophosphamide
ACE inhibitor	angiotensin converting enzyme inhibitor
ACT	doxorubicin (Adriamycin) and cyclophosphamide followed by paclitaxel (Taxol)
ACTH	doxorubicin (Adriamycin) and cyclophosphamide followed by paclitaxel (Taxol) and trastuzumab (Herceptin)
AC→WP	doxorubicin (Adriamycin) and cyclophosphamide followed by weekly paclitaxel (Taxol)
AC→WP+H→H	doxorubicin (Adriamycin) and cyclophosphamide followed by weekly paclitaxel (Taxol) and trastuzumab (Herceptin) followed by trastuzumab (Herceptin)
ADCC	antibody-dependent cell-mediated cytotoxicity
ADL	activities of daily living
AE	adverse event
AMH	anti-Müllerian hormone
ANC	absolute neutrophil count
ARB	angiotensin II receptor blocker
ARDS	acute respiratory distress syndrome
ASCO	American Society of Clinical Oncology
AST (SGOT)	aspartate aminotransferase
AT	doxorubicin (Adriamycin) and docetaxel (Taxotere)
BAHO	Behavioral and Health Outcomes
BCFS	breast cancer-free survival
BCIRG	Breast Cancer International Research Group
BMI	body mass index
BP	blood pressure
BSA	body surface area
BWFI	bacteriostatic water for injection
CAEPR	Comprehensive Adverse Event and Potential Risks
CAF	cyclophosphamide, doxorubicin (Adriamycin), fluorouracil
CAP	College of American Pathologists
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CEF	cyclophosphamide, epirubicin, fluorouracil
CHF	congestive heart failure
CI	confidence interval
CISH	chromagen in situ hybridization
CMF	cyclophosphamide, methotrexate, fluorouracil
CRA	chemotherapy-related amenorrhea
CRP	C-reactive protein
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP-Adverse Event Reporting System
CTEP-IAM	CTEP-Identity and Access Management
CTSU	Cancer Trials Support Unit
DBCG	Danish Breast Cancer Group
D/C	discontinue

GLOSSARY OF SELECTED ABBREVIATIONS AND ACRONYMS (continued)

DCIS	ductal carcinoma in situ
DCTD	Division of Cancer Treatment and Diagnosis
DFS	disease-free survival
DMC	Data Monitoring Committee
DRFI	distant recurrence-free interval
DTC	disseminated tumor cells
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECG	electrocardiogram
EpCAM	epithelial cell adhesion molecule
ER	estrogen receptor
ErbB2	epidermal growth factor receptor 2
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
GnRH	gonadotropin-releasing hormone
GWAS	genome-wide association study
H	trastuzumab (Herceptin)
H&E	hematoxylin and eosin
HER2	human epidermal growth factor receptor 2
HERA	Herceptin Adjuvant Trial
HR	hazard ratio
IB	Investigator's Brochure
IBTR	ipsilateral breast tumor recurrence
ICORG	All Ireland Co-operative Oncology Research Group
IDB	Investigational Drug Branch
IDFS	invasive disease-free survival
IHC	immunohistochemistry
IND	investigational new drug
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
LBA	ligand-binding assay
LCIS	lobular carcinoma in situ
LHRH	luteinizing hormone-releasing hormone
LLN	lower limit of normal
LV	left ventricular
LVEF	left ventricular ejection fraction
MAF	minor allele frequency
mg	milligram
mg/m^2	milligrams per meter squared
MH	menstrual history
MI	myocardial infarction
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

GLOSSARY OF SELECTED ABBREVIATIONS AND ACRONYMS (continued)

MSKCC	Memorial Sloan-Kettering Cancer Center
MUGA	multigated acquisition (scan)
n	sample size
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NCTN	National Clinical Trials Network
NK	natural killer
NOS	not otherwise specified
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSAID	non-steroidal anti-inflammatory drug
NSC	National Service Center
OPEN	Oncology Patient Enrollment Network
OR	overall response
OS	overall survival
P	paclitaxel
p	probability
PAF	L-phenylalanine mustard, doxorubicin, fluorouracil
PASS	Power Analysis and Sample Size
PET	positron emission tomography
PF	L-phenylalanine mustard, fluorouracil
PFS	progression-free survival
PgR	progesterone receptor
pHER2	phosphorylated HER2
PMB	Pharmaceutical Management Branch
PTEN	phosphatidylinositol phosphate 3'-phosphatase
QRT-PCR	quantitative real-time reverse transcription-polymerase chain reaction
RFI	recurrence-free interval
RNA	ribonucleic acid
RR	relative risk
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
RT-PCR	reverse transcription-polymerase chain reaction
SABCS	San Antonio Breast Cancer Symposium
SDMC	Statistics and Data Management Center
SERM	selective estrogen receptor modulator
SN	sentinel node
SNP	single nucleotide polymorphism
SQ, SC	subcutaneous
SWFI	sterile water for injection
TAC	docetaxel (Taxotere), doxorubicin (Adriamycin), and cyclophosphamide
TC	docetaxel (Taxotere) and cyclophosphamide
TCH	docetaxel (Taxotere), carboplatin, and trastuzumab (Herceptin)
TC+H→H	docetaxel (Taxotere), cyclophosphamide, and trastuzumab (Herceptin) followed by trastuzumab (Herceptin)
Topo IIA	topoisomerase II alpha
ULN	upper limit of normal

GLOSSARY OF SELECTED ABBREVIATIONS AND ACRONYMS (continued)

uPAR	urokinase receptor, plasminogen activator
USON	US Oncology, Inc.
WP	weekly paclitaxel
WP+H	weekly paclitaxel and trastuzumab

1.0 OVERVIEW OF THE STUDY DESIGN

Note: Accrual closed on February 10, 2015, following achievement of the sample size goal.

NSABP B-47, a Phase III, multicenter, open-label, randomized adjuvant therapy trial, will compare the value of adding trastuzumab to chemotherapy relative to chemotherapy without trastuzumab in women with resected node-positive or high-risk node-negative HER2-low invasive breast cancer. For the B-47 trial, HER2-low is defined as either an IHC score of 1+ or an IHC score of 2+ *with* negative in situ hybridization.

This trial will determine whether the addition of trastuzumab to standard chemotherapy regimens improves invasive disease-free survival relative to chemotherapy alone. Secondary aims include determining whether the addition of trastuzumab to chemotherapy improves disease-free survival, breast cancer-free survival, recurrence-free interval, distant recurrence-free interval, and overall survival relative to chemotherapy alone. Additionally, the toxicities of the regimens will be compared.

The investigator must indicate at the time of study entry which of the two B-47 chemotherapy regimens the patient will receive. The non-anthracycline regimen (for patients in Groups 1A and 2A) is TC (docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2) administered IV every 3 weeks for 6 cycles. The anthracycline regimen (for patients in Groups 1B and 2B) is AC$\rightarrow$WP (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 administered IV either every 3 weeks or every 2 weeks [per investigator discretion] for 4 cycles followed by paclitaxel 80 mg/m^2 IV administered weekly for 12 doses).

Patients will be randomized to receive chemotherapy with or without trastuzumab therapy. For patients receiving the TC chemotherapy regimen, trastuzumab will be given every 3 weeks during and following chemotherapy until 1 year after the first trastuzumab dose (8 mg/kg loading dose; 6 mg/kg for the remaining doses). For patients receiving the AC$\rightarrow$WP chemotherapy regimen, trastuzumab will begin with the first dose of weekly paclitaxel and will be given weekly for 12 doses (4 mg/kg loading dose; 2 mg/kg for the remaining weekly doses). Following completion of WP, trastuzumab will continue with 6 mg/kg doses given every 3 weeks for a total of 1 year of trastuzumab therapy. Patients will also receive adjuvant radiation therapy and endocrine therapy, as clinically indicated.

Menopausal status will be determined at baseline for all patients. Women who have had a menstrual period within 12 months before randomization (and have not had a hysterectomy) will have menstrual history information collected at 3 and 6 months and then every 6 months until 3 years after randomization. Additionally, women in this menstrual history cohort will also be asked to consent to blood sample collection at baseline and follow-up time points until 2 years after randomization. Samples will be assayed for estradiol, FSH, and anti-Müllerian hormone to provide biological correlates of amenorrhea and to examine the interaction of chemotherapy regimens, trastuzumab, and endocrine therapies with menstrual status as determined by biological evaluation and menstrual history data. In addition, blood samples will be prepared and isolated into DNA, RNA, plasma, and serum for future research studies on those women who became amenorrheic with therapy versus those who did not to better inform potential biological and hormonal factors that may be responsible for the beneficial effects of amenorrhea. DNA from blood samples will be used for comprehensive genotyping to assess for genetic predictors of chemotherapy-related amenorrhea.

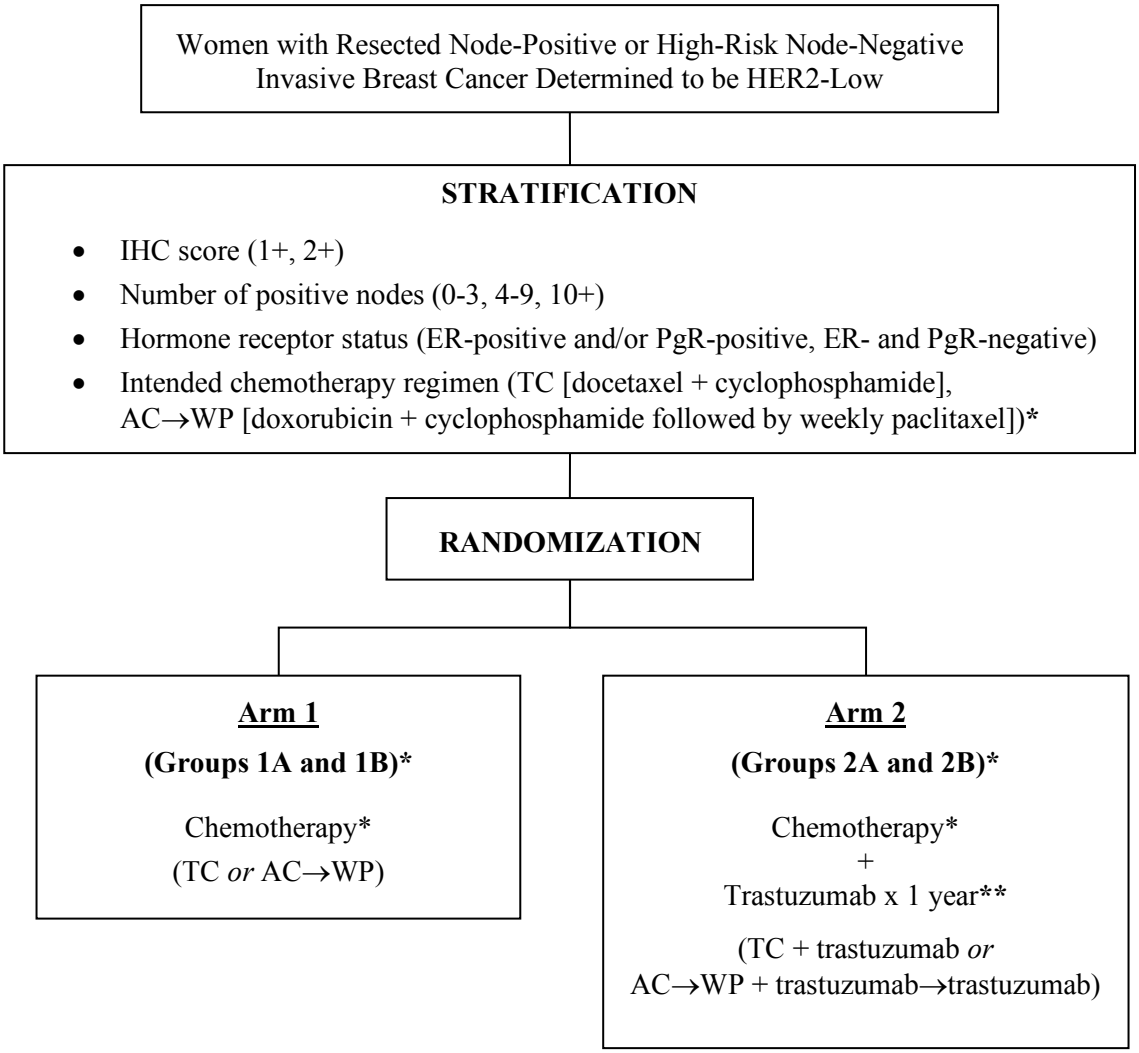
In addition, other host factors that may influence the risk for cancer recurrence will be examined in the *entire B-47 study population*, including comorbid conditions, medications that may have systemic effects on inflammatory processes (e.g., metformin, beta blockers, ARBs, ACE inhibitors, and aspirin), weight and weight gain, and tobacco and alcohol use. For all B-47

patients (who consented to submission of optional blood samples), plasma C-reactive protein will be assessed at baseline (pre-treatment) and at one year after randomization.

Tumor blocks must be submitted for correlative science studies, which will include the evaluation of molecular and other predictors of the benefit of adding trastuzumab to chemotherapy for patients with HER2-low breast cancer. Submission of a tumor sample is a study requirement for all patients. Tumor samples will be used to test hypotheses related to the use of trastuzumab for HER2-low breast cancer. These hypotheses address the predictive effect of tumor cell gene expressions and putative therapeutic immunologic mechanisms. Also, additional blood samples from all B-47 patients who have consented to optional blood sample submission will be collected before therapy begins and at 1 year following randomization. These samples will be used to identify predictors of trastuzumab benefit.

The B-47 study will enroll 3,260 patients over a period of approximately 3 years and 2 months. It is anticipated that the definitive analysis will be carried out approximately 6 years after study initiation.

Figure 1.
NSABP B-47 SCHEMA



* At the time of study entry, the investigator must designate which of the following two chemotherapy regimens will be administered:

- **Chemotherapy regimen A for Groups 1A and 2A**

  TC: Docetaxel 75 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 3 weeks for 6 cycles.

- **Chemotherapy regimen B for Groups 1B and 2B**

  AC→WP: Doxorubicin 60 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 IV weekly for 12 doses; at the investigator's discretion, doxorubicin/cyclophosphamide may be administered every 2 weeks for 4 cycles (dose-dense schedule).

** Trastuzumab:

- Given with TC **(Group 2A)**: 8 mg/kg loading dose on Day 1 of Cycle 1 of TC; then 6 mg/kg IV cycles 2–6. After completion of TC, trastuzumab will continue with 6 mg/kg IV every 3 weeks for 11 doses.
- Given with AC → WP **(Group 2B)**: 4 mg/kg loading dose beginning with the first dose of weekly paclitaxel; then 2 mg/kg weekly for a total of 12 weekly doses; after completion of WP, trastuzumab will continue with 6 mg/kg doses IV every 3 weeks for a maximum of 13 doses.

2.0 BACKGROUND

2.1 Introduction

The joint analysis of NSABP B-31/NCCTG 9831 demonstrated major reductions in disease recurrence and death from HER2-gene-amplified or protein-overexpressing breast cancer with the incorporation of a year of trastuzumab into a standard AC→paclitaxel adjuvant chemotherapy regimen. These findings, confirmed by BCIRG 006 and HERA, changed the standard of adjuvant therapy for women with the HER2-positive breast cancer.[1-3] Central testing of specimens from patients enrolled in NSABP B-31 demonstrated that 174 of 1787 (9.7%) cases had neither gene amplification nor overexpression of HER2. Surprisingly, these patients appeared to derive similar benefit from the addition of trastuzumab to patients with tumors that were centrally confirmed as HER2-positive (RR for DFS=0.34 95% CI: 0.14-0.80; p=0.014). A study to validate the central testing findings by three independent pathologists confirmed the apparent benefit from trastuzumab in a subset of patients from this cohort for whom specimens were available (RR for DFS=0.34; 95% CI: 0.14-0.80; p=0.039).[4]

Comprehensive correlative science studies utilizing archived tumor tissue blocks from B-31 have demonstrated provocative results: 1) HER2 mRNA expression level but not HER2 gene copy number (by FISH) showed a significant statistical interaction with trastuzumab, confirming HER2 as a treatment target. A lower expression level of HER2 mRNA was associated with lesser degree of benefit from trastuzumab. However, when the mRNA cut-off for trastuzumab benefit was applied to expression in HER2-negative breast cancers, a significant proportion of HER2-negative tumors expressed HER2 mRNA levels above the cut-off. 2) Candidate markers identified from the metastatic disease setting such as PI-3-Kinase gene mutation or loss of PTEN were not associated with resistance to trastuzumab.

Together, these data suggest that there may be important differences in the mechanism of action of trastuzumab in the adjuvant setting compared to the metastatic disease setting and that the threshold of HER2 expression for benefit from adjuvant trastuzumab added to standard chemotherapy may be much lower than that observed in the metastatic disease setting.

NSABP Protocol B-47 will determine if these provocative, unexpected findings can be confirmed in a prospective, Phase III trial supported by extensive correlative science studies to understand how trastuzumab might improve invasive disease-free survival (IDFS) and overall survival (OS) in women diagnosed with breast cancer regarded as HER2-negative by the ASCO/CAP HER2 Testing Guidelines.[5]

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2.8 Choice of chemotherapy

The information summarized earlier suggests that the potential benefit of trastuzumab in the adjuvant therapy of early HER2-low breast cancer would be achieved when administered in combination with chemotherapy. Results of four large Phase III trials evaluating the role of trastuzumab incorporated into standard anthracycline-based adjuvant chemotherapy regimens in women with HER2-positive breast cancer defined by standard criteria have demonstrated a consistent 30–50% reduction in hazard for DFS events 3-4 years following randomization along with a 35–40% reduction in risk for mortality.[1-3] These remarkable benefits were achieved without an increase in toxicity, with the important exception of low rates of congestive heart failure ranging from 1.9–3.8%.[1-3,41] Predictive factors for increased risk of severe cardiac toxicity were evaluated in NSABP B-31 and NCCTG N9831. In the B-31 population, age > 50 years (p=0.03), the need for hypertension medication at entry (p=0.02), and baseline LVEF below 55% (p=0.0003) were predictors for a cardiac event. Women < 50 years had a risk of 2.3%, women aged 50 to 59 had a risk of 5.1%, and women ≥ 60 years had a risk of 5.4%. The need for hypertension medication is also a predictor for a cardiac event and increased the risk to 6.8%. The major increase in risk occurred in women with baseline LVEF within the normal range but with a value < 55%. Their 5-year cumulative risk was 12.9%.[43] The analysis of risk factors for a cardiac event from N9831 supported the findings of B-31. Women ≥ 60 years had a risk of 6.6%, women aged 50 to 59 years had a 2.8% risk, and women < 50 years had a 2.1% risk (p=0.003). Previous or current use of antihypertensive agents increased the risk to 6.0% (p=0.005). Baseline LVEF above the LLN but < 55% increased the risk to 5.6% (p=0.033).[44]

BCIRG 006 evaluated a non-anthracycline arm consisting of docetaxel, carboplatin, and trastuzumab (TCH) and reported an HR for DFS of 0.67 (CI: 0.54–0.83; p=0.0003) relative to a control regimen of AC followed by docetaxel.[1] The DFS HR for the investigational anthracycline-based chemotherapy regimen adding trastuzumab to AC followed by docetaxel relative to the chemotherapy alone was 0.61 (CI: 0.48–0.76; p<0.0001). At this time, the results achieved with the two trastuzumab arms are indistinguishable in terms of efficacy. However, the

rate of CHF reported with the TCH regimen was only 0.4%. Thus, omission of the anthracycline markedly reduced the rate of the major toxicity of trastuzumab, without reducing the apparent benefit.

Since the B-47 study will evaluate the role of trastuzumab in the adjuvant therapy of a patient population with HER2-low breast cancer, it will be important to employ chemotherapy regimens with very low rates of cardiac toxicity when combined with trastuzumab and which are considered as standards of care when used without trastuzumab in patient populations with HER2-negative disease. We propose to allow investigators the choice of employing docetaxel 75 mg/m^2 plus cyclophosphamide 600 mg/m^2 (TC) every 3 weeks for 6 cycles or an anthracycline regimen of AC→WP (doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 administered IV every 14 days or every 21 days for 4 cycles followed by paclitaxel 80 mg/m^2 IV administered weekly for 12 doses). Patients will be randomized to receive chemotherapy with or without trastuzumab therapy.

2.8.1 *Rationale for non-anthracycline chemotherapy option of TC*

We propose to use a non-anthracycline chemotherapy regimen as one of the chemotherapy treatment options based upon two considerations: 1) It does not appear that the distinct subtype of HER2 non-amplified breast cancer benefits substantially from anthracyclines, and 2) cardiotoxicity considerations are of major importance in this study.

Anthracyclines have been used in most standard adjuvant chemotherapy regimens for decades. Early clinical trials of unselected higher risk breast cancer cohorts of all subtypes showed improved outcomes when an anthracycline regimen was compared to a similar regimen without an anthracycline (CEF vs. CMF, CAF vs. CMF, PAF vs. PF).[45] The modest outcome advantage was previously thought to be shared by the entire cohort. The EBCTCG overview of 16,000+ participants confirmed the benefit of adjuvant anthracyclines in breast cancer patients unselected for gene expression subtype.[46] The recent recognition that the main target of anthracyclines is the topoisomerase II alpha (topo IIA) protein now allows anthracycline chemotherapy to be considered a targeted therapy.[47-49] The majority (88–98%) of topo IIA alterations (mostly amplifications but some deletions) occur in the HER2-positive gene-amplified subset of breast cancers.[50] The topo IIA gene is in very close proximity to the HER2 gene on chromosome 17, and they are commonly in the same amplicon.

O'Malley et al studied the benefit of epirubicin in the NCIC MA.5 trial and demonstrated that the previously shown modest benefit in DFS and OS of CEF over CMF can be explained by a large benefit confined to the subset of patients with topo IIA alterations.[50] No benefit was seen in patients with the non-altered topo IIA. HER2-positive gene amplification and topo IIA amplifications/alterations were highly associated in this population, as expected.

While the updated overview analyses conducted in 2005/2006 by the EBCTCG continue to show benefits of anthracycline-based chemotherapy regimens relative to non-anthracycline, non-taxane-based regimens (absolute reduction in risk for recurrence at 10 years of 2.9% and an absolute reduction in mortality of 3.2%),[51] results of retrospective analyses such as above, of tumor specimens from patients treated in prospective, randomized trials (NSABP B-11, NSABP B-15, NCIC MA.5, DBCG 89-D studies, and others) evaluating the benefits of adding an anthracycline to cyclophosphamide-based regimens have consistently demonstrated that the benefit

appears to be largely limited to the subset of patients with HER2-overexpressing breast cancers.[52-59] Prospective randomized trials to address these retrospective findings have not been completed. A trial to compare TC to TAC in patients with HER2-negative tumors is underway.

The US Oncology (USON) trial 9735 compared TC to standard AC in 1016 women with node-positive or high-risk, node-negative operable breast cancer. Patients were randomly assigned to 4 cycles of either standard-dose AC x 4 cycles (60/600 mg/m^2) [n=510] or TC x 4 cycles (75/600 mg/m^2) [n=506], administered every 3 weeks. After a median follow-up of 7 years, DFS was statistically superior for TC relative to AC, 81% vs. 75% (HR=0.74; p=0.033), and the survival difference between TC and AC was significant, 87% and 82% (HR=0.69; p=0.032).[60] The TC arm was associated with more myalgias, arthralgias, edema, and febrile neutropenia, while patients on the AC arm experienced more nausea and vomiting. In the AC group, one patient died from CHF and four patients from MI. In the TC group, no cases of CHF were observed though two patients had an MI.[61,62] An exploratory analysis of DFS according to age, hormone-receptor status, and nodal status demonstrated that the benefit was present in all subsets.[61] Jones et al also presented data at the 2009 SABCS evaluating toxicity of the TC regimen combined with trastuzumab in 260 patients with the HER2+ breast cancer subtype. Nine patients (3.4%) discontinued trastuzumab due to decreases in ejection fraction. Sixteen patients (6.1%) had declines of LVEF below 50% during treatment. No patients experienced CHF.[63]

The average age at presentation of HER2 non-amplified breast cancer is older than the average age for HER2 amplified breast cancer (average age of a B-31 patient at entry was 49 years old). Since age over 60 is a risk factor of trastuzumab cardiotoxicity, there are many women over this age with HER2 non-amplified breast cancer who might potentially benefit from trastuzumab but would face increased cardiotoxicity risk. Since this trial will specifically target patients with tumors that do not overexpress HER2, the non-anthracycline TC regimen (which has demonstrated superiority to AC in patients not selected for HER2 status) represents an appropriate adjuvant chemotherapy regimen option for the patients in B-47.

2.8.2 *Rationale for duration of TC chemotherapy to be 6 cycles*

NSABP B-30 enrolled 5351 women with node-positive breast cancer and was enrolling patients during the same time period as B-31. The study compared AC x 4 followed by docetaxel x 4 vs. TAC x 4 vs. AT x 4. The primary aim of the study was to determine if there was a significant difference in OS in the AC→T vs. TAC x 4 arms. There was a trend toward superiority of AC→T vs. TAC with a HR of 0.86 (p=0.086) for OS. AC→T was superior to TAC x 4 for reduction in DFS events with a HR of 0.83 (p=0.006). Toxicities were similar in AC→T and TAC with the notable exception that febrile neutropenia was more frequent in the AC→T arm (22% vs. 16%; p=0.0001). However, primary prophylaxis with G-CSF was required in the TAC arm, but not in the AC→T arm.[64] The difference in treatment cycles delivered (8 vs. 4) may be a likely explanation for the difference in DFS seen.

In BCIRG 005, TAC x 6 was compared with sequential AC x 4 followed by docetaxel x 4 (similar to the B-30 arm with AC followed by docetaxel) in 3298 women with node-positive, HER2-normal breast cancer. The primary endpoint of DFS showed no difference between the arms (HR=1.002 95% CI 0.86–1.16). The TAC arm administered

without primary G-CSF prophylaxis had a significantly higher rate of febrile neutropenia (17.9% vs. 8.3%; p< 0.0001) and thrombocytopenia (2.5% vs. 1.3%; p=0.01) than AC→T, while the AC→T arm had a greater incidence of neuropathy, nail changes, and myalgias.[26] The equivalency seen in the BCIRG 005 study may have been a result of a higher number of chemotherapy cycles in TAC x 6.[65]

The successful adjuvant trastuzumab trials utilized 6–8 cycles of chemotherapy including B-31 (8 cycles). Although USON 9735 used only 4 cycles of chemotherapy, we have chosen to use 6 cycles of TC in order to more closely emulate the B-31 study and the TC component of TAC in BCIRG 005.

2.8.3 *Rationale for anthracycline chemotherapy option of AC→WP*

The results of USON 9735,[66] the evolving long-term anthracycline cardiotoxicity data, and the emerging evidence of the targeted nature of anthracycline therapy have initiated an ongoing question regarding the continued role of anthracyclines in the adjuvant chemotherapy of HER2-negative breast cancer. While topo IIA represents a critical target of anthracyclines, the activity cannot be explained solely by inhibition of topo IIA. Additionally, topo IIA is expressed by tumors with high proliferation rates, so the possibility of benefit in the subset of patients with tumors that are HER2-negative, but have a high proliferation rate, remains unclear.[67] Data from B-31 and N9831 indicate that younger patients without hypertension and with baseline LVEFs above 55% have a low risk for cardiac toxicity even with the sequential AC→PH regimens.[43,44] A trial conducted by the MSKCC demonstrated that the administration of dose-dense AC followed by WPH does not appear to increase the risk of cardiac toxicity over the non-dose-dense schedule of AC, and dose-dense administration of AC→P appears to offer advantages in patients with triple-negative breast cancer.[68] Thus, investigators and younger women with high risk breast cancer may prefer AC→WP as a regimen relative to TC.

The primary aim of B-47 is to determine the benefit of adding trastuzumab to chemotherapy in this patient population. It is not expected that there will be differential trastuzumab benefits based on the choice of TC or AC→WP. However, to avoid imbalance between the chemotherapy options, chemotherapy choice will be a stratification factor. Provision for investigator choice of chemotherapy will support optimal enrollment rates and minimize risk for selective exclusion of high-risk patients due to concerns about lack of an anthracycline option.

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3.0 STUDY AIMS AND ENDPOINTS

3.1 Primary aim and endpoint

Aim: To determine whether the addition of trastuzumab to chemotherapy (TC *or* AC→WP) improves ***invasive*** disease-free survival (IDFS) in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

Endpoint: IDFS, defined as time to local invasive recurrence following mastectomy, local invasive recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral invasive breast cancer, second non-breast primary cancer (excluding squamous or basal cell carcinoma of the skin), or death from any cause prior to recurrence or second primary cancer.[97]

3.2 Secondary aims and endpoints

3.2.1 *Disease-free survival (DFS-DCIS)*

Aim: To determine whether the addition of trastuzumab to chemotherapy (TC *or* AC→WP) improves DFS-DCIS in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

Endpoint: DFS-DCIS, defined as time to local recurrence following mastectomy, local recurrence (invasive or DCIS) in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral breast cancer (invasive or DCIS), invasive second primary cancer (excluding squamous and basal cell carcinoma of the skin), or death from any cause prior to recurrence or second primary cancer.[97]

3.2.2 *Breast cancer-free survival (BCFS)*

Aim: To determine whether the addition of trastuzumab to chemotherapy (TC *or* AC→WP) improves BCFS in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

Endpoint: BCFS, defined as time from randomization until local recurrence (invasive or DCIS), regional recurrence, or distant recurrence, contralateral breast cancer (invasive or DCIS), or death from any cause.

3.2.3 *Recurrence-free interval (RFI)*

Aim: To determine whether the addition of trastuzumab to chemotherapy (TC *or* AC→WP) improves RFI in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

Endpoint: RFI, defined as time from randomization until invasive local, regional, or distant recurrence, or death from breast cancer (censored for deaths from other causes).[97]

3.2.4 ***Distant recurrence-free interval (DRFI)***

Aim: To determine whether the addition of trastuzumab to chemotherapy (TC *or* AC→WP) improves DRFI in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

Endpoint: DRFI, defined as time from randomization until the first diagnosis of distant metastasis or death from breast cancer, regardless of occurrence of any intervening local or regional recurrences, contralateral breast cancers, or non-breast second primary cancers. This endpoint is censored at the time of death from causes other than breast cancer.[97]

3.2.5 ***Overall survival (OS)***

Aim: To determine whether the addition of trastuzumab to chemotherapy (TC *or* AC→WP) improves OS in women with resected node-positive or high-risk node-negative breast cancer which is reported as HER2-low by all HER2 testing performed.

Endpoint: OS, defined as time from randomization to death from any cause.

3.2.6 ***Menstrual history***

Aim: To evaluate the associations between amenorrhea and circulating reproductive hormone levels, and the associations between chemotherapy regimen, amenorrhea, and IDFS benefit in premenopausal women eligible at baseline for the menstrual history assessments.

Endpoint: Amenorrhea, circulating reproductive hormone suppression, and IDFS as defined in Section 17.9.

3.2.7 ***Toxicity***

Aim: To evaluate the toxicity associated with each of the regimens.

Endpoint: Frequencies of adverse events categorized using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).

3.2.8 ***Molecular predictors of efficacy***

Aim: To test the hypothesis that the HER2 mRNA level is the predictor of the degree of benefit from trastuzumab and the threshold for benefit in the adjuvant setting is lower than defined by current ASCO/CAP Guidelines for HER2 assays (IHC and FISH).

Aim: To identify and/or validate molecular predictors of the degree of benefit from the addition of trastuzumab to chemotherapy (TC *or* AC→WP).

Aim: To test the alternative hypothesis that the main determinant of trastuzumab response in the adjuvant setting of HER2-low breast cancer is through ADCC by demonstrating that the polymorphism of the Fcγ receptor gene is predictive of the degree of benefit from the addition of trastuzumab to chemotherapy (TC *or* AC→WP).

3.2.9 ***Inflammatory correlates of outcome***

Aim: To examine the relationship between behavioral host factors (obesity, tobacco, alcohol) and comorbid conditions that may influence systemic inflammation and breast cancer outcomes, controlling for tumor/stage characteristics and treatment assignment.

Aim: To examine the relationship between medication exposures that may influence systemic inflammation and breast cancer outcomes, controlling for tumor/stage characteristics and treatment assignment.

Aim: To examine the relationship between comorbid conditions, medication exposures and behavioral host factors together and breast cancer outcomes, controlling for tumor/stage characteristics and treatment assignment.

4.0 PATIENT ELIGIBILITY AND INELIGIBILITY

Note: Accrual closed on February 10, 2015, following achievement of the sample size goal.

4.1 Patient selection guidelines

Although the guidelines in Section 4.1 are not inclusion/exclusion criteria, investigators should consider each of these factors when selecting patients for the trial. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

- Patients should have a life expectancy of at least 10 years, excluding their diagnosis of breast cancer. (Comorbid conditions should be taken into consideration, but not the diagnosis of breast cancer.)
- Women of reproductive potential must agree to use an effective non-hormonal method of contraception (for example condoms, some intrauterine devices, diaphragms, tubal ligation, vasectomized partner, or abstinence) during therapy ***and for at least 6 months (Arm 1 patients) and for at least 7 months (Arm 2 patients) after the last dose of study therapy (chemotherapy or trastuzumab)***.
- ***Submission of tumor samples from the breast surgery is required for all patients*** (see Section 7.1). Therefore, the local pathology department policy regarding release of tumor samples must be considered in the screening process. Patients whose tumor samples are located in a pathology department that by policy will not submit any samples for research purposes should not be approached for participation in the B-47 trial.

4.2 Conditions for patient eligibility

A patient cannot be considered eligible for this study unless all of the following conditions are met.

4.2.1 The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

4.2.2 The patient must be female.

4.2.3 The patient must be ≥ 18 years old.

4.2.4 The patient must have an ECOG performance status of 0 or 1 (see ***Appendix A***).

4.2.5 The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination.

4.2.6 All of the following staging criteria (according to the 7th edition of the AJCC Cancer Staging Manual) must be met:

- By pathologic evaluation, primary tumor must be pT_{1-3};
- By pathologic evaluation, ipsilateral nodes must be pN_0, pN_1 (pN_{1mi}, pN_{1a}, pN_{1b}, pN_{1c}), pN_{2a}, pN_{2b}, pN_{3a}, or pN_{3b}

If pN_0, *one* of the following criteria must be met:

- pT_2 ***and*** ER negative ***and*** PgR negative; ***or***
- pT_2 ***and*** ER positive (PgR status may be positive or negative) ***and*** either grade 3 histology or Onco*type* DX® Recurrence Score of ≥ 25; ***or***
- pT_3 regardless of hormone receptor status, histologic grade, and Onco*type* DX® Recurrence Score.

4.2.7 HER2 status of the primary tumor must be evaluated prior to randomization; all testing performed must indicate that the tumor is HER2-low as defined below.

- **IHC must be performed** and the IHC staining results must indicate a score of 1+ (in situ hybridization [ISH] testing is not required) or 2+ (ISH must also be performed and must indicate that the tumor is HER2-low as described below).
- If ISH testing is performed, test results must be as follows ***and*** IHC must be 1+ or 2+: The ratio of HER2 to *CEP17* must be < 2.0 or, if a ratio was not performed, the HER2 gene copy number must be < 4 per nucleus.

Note: If the IHC staining intensity is reported as a range, e.g., 0 to 1+ or 1+ to 2+, the higher intensity score in the range should be used to determine eligibility.

4.2.8 The patient must have undergone either a total mastectomy or breast-conserving surgery (lumpectomy). (Patients who have had a nipple-sparing mastectomy are eligible.)

4.2.9 For patients who undergo lumpectomy, the margins of the resected specimen must be histologically free of invasive tumor and DCIS as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. (Patients with margins positive for LCIS are eligible without additional resection.)

4.2.10 For patients who undergo mastectomy, margins must be free of gross residual tumor. (Patients with microscopic positive margins are eligible as long as post-mastectomy RT of the chest wall will be administered.)

The patient must have completed ***one of the procedures*** for evaluation of pathologic nodal status listed below.

- Sentinel lymphadenectomy alone:
  - If pathologic nodal staging based on sentinel lymphadenectomy is pN_0 or pN_{1b};
  - If pathologic nodal staging based on sentinel lymphadenectomy is pN_{1mi} or pN_{1a}, the primary tumor must be T_1 or T_2 by pathologic evaluation and the nodal involvement must be limited to 1 or 2 positive nodes.
- Sentinel lymphadenectomy followed by removal of additional non-sentinel lymph nodes if the sentinel node (SN) is positive; or
- Axillary lymphadenectomy with or without SN isolation procedure.

4.2.11 The interval between the last surgery for breast cancer (treatment or staging) and randomization must be no more than 84 days.

4.2.12 The patient must have ER analysis performed on the primary tumor prior to randomization. If ER analysis is negative, then PgR analysis must also be performed. (Either the core biopsy or surgical resection specimen can be used for ER/PgR testing.) Patients with a primary tumor that is hormone receptor-positive or receptor-negative are eligible.

4.2.13 The most recent postoperative blood counts, performed within 6 weeks prior to randomization, must meet the following criteria:

- ANC must be ≥ 1200/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and
- Hemoglobin must be ≥ 10 g/dL.

4.2.14 The following criteria for evidence of adequate hepatic function must be met based on the results of the most recent postoperative tests performed within 6 weeks prior to randomization:

- total bilirubin must be ≤ ULN for the lab unless the patient has a bilirubin elevation > ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and*
- alkaline phosphatase must be ≤ 2.5 x ULN for the lab; *and*
- AST must be ≤ 1.5 x ULN for the lab.
- *Alkaline phosphatase and AST may not both be > the ULN*. For example, if the alkaline phosphatase is > the ULN but ≤ 2.5 x ULN, the AST must be ≤ the ULN. If the AST is > the ULN but ≤ 1.5 x ULN, the alkaline phosphatase must be ≤ ULN.

Note: If ALT is performed instead of AST (per institution's standard practice), the ALT value must be ≤ 1.5 x ULN; if both were performed, the AST must be ≤ 1.5 x ULN.

4.2.15 Patients with AST or alkaline phosphatase > ULN are eligible for inclusion in the study if liver imaging (CT, MRI, PET-CT, or PET scan) performed within 90 days prior to randomization does not demonstrate metastatic disease and the requirements in criterion 4.2.15 are met.

4.2.16 Patients with alkaline phosphatase that is > ULN but ≤ 2.5 x ULN or unexplained bone pain are eligible for inclusion in the study if a bone scan, PET-CT scan, or PET scan performed within 90 days prior to randomization does not demonstrate metastatic disease.

4.2.17 The most recent postoperative serum creatinine performed within 6 weeks prior to randomization must be ≤ ULN for the lab.

4.2.18 LVEF assessment must be performed within 90 days prior to randomization. LVEF assessment performed by 2-D echocardiogram is preferred; however, MUGA scan may be substituted based on institutional preferences.

- For patients who will receive the **TC chemotherapy regimen, the LVEF must be ≥ 50%** regardless of the cardiac imaging facility's lower limit of normal.
- For patients who will receive the **AC→WP chemotherapy regimen, the LVEF must be ≥ 55%** regardless of the cardiac imaging facility's lower limit of normal.

Note: Since the pre-entry LVEF serves as the baseline for comparing subsequent LVEF assessments, it is critical that this baseline study be an accurate assessment. If the baseline LVEF is > 70%, the investigator is encouraged to have the accuracy of the initial LVEF result confirmed and repeat the test if the accuracy is uncertain. (See Sections 5.2 and 5.3 for LVEF instructions.)

4.3 Conditions for patient ineligibility

Patients with one or more of the following conditions are NOT eligible for this study.

4.3.1 ***Primary tumor with any of the following HER2 testing results:***

- IHC staining intensity:
- 0 on ***all*** evaluations of specimens
- 3+ on evaluation of ***any*** specimen
- ISH with a ratio of HER2 to *CEP17* ≥ 2.0 on evaluation of ***any*** specimen
- ISH result indicating HER2 gene copy number ≥ 4 per nucleus on evaluation of ***any*** specimen.

4.3.2 T4 tumors including inflammatory breast cancer.

4.3.3 Definitive clinical or radiologic evidence of metastatic disease. (Note: Chest imaging [mandatory for all patients] and other imaging [if required] must have been performed within 90 days prior to randomization.)

4.3.4 Synchronous or previous contralateral invasive breast cancer. (Patients with synchronous and/or previous contralateral DCIS or LCIS are eligible.)

4.3.5 Any previous history of ipsilateral invasive breast cancer or ipsilateral DCIS. (Patients with synchronous or previous ipsilateral LCIS are eligible.)

4.3.6 History of *non-breast* malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to randomization.

4.3.7 Previous therapy with anthracyclines, taxanes, or trastuzumab for any malignancy.

4.3.8 Chemotherapy or HER2-targeted therapy administered for the currently diagnosed breast cancer prior to randomization.

4.3.9 Whole breast RT prior to randomization or partial breast RT that cannot be completed on or before the date of randomization (see Section 9.8 and 9.10.3).

4.3.10 Continued endocrine therapy such as raloxifene or tamoxifen (or other SERM) or an aromatase inhibitor. Patients are eligible if these medications are discontinued prior to randomization (see Section 9.9).

4.3.11 Any continued use of sex hormonal therapy, e.g., birth control pills, ovarian hormone replacement therapy. Patients are eligible if these medications are discontinued prior to randomization (see Section 4.1).

4.3.12 Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens. This includes but is not confined to:

Active cardiac disease

- angina pectoris that requires the current use of anti-anginal medication;
- ventricular arrhythmias except for benign premature ventricular contractions;
- supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
- conduction abnormality requiring a pacemaker;
- valvular disease with documented compromise in cardiac function; and
- symptomatic pericarditis.

History of cardiac disease

- myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
- history of documented CHF; and
- documented cardiomyopathy.

4.3.13 Hypertension defined according to the following ineligibility criteria:

- For patients who will receive ***TC*** (regardless of the patient's age): Uncontrolled hypertension defined as sustained systolic BP > 150 mmHg *or* diastolic BP > 90 mmHg. (Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria.)
- For patients ***< 50 years*** old who will receive ***AC→WP***: Uncontrolled hypertension defined as sustained systolic BP > 150 mmHg *or* diastolic BP > 90 mmHg. Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria.
- For patients ***≥ 50 years*** old who will receive ***AC→WP***:
  - Uncontrolled hypertension defined as sustained systolic BP > 150 mmHg *or* diastolic BP > 90 mmHg.
  - Controlled hypertension (systolic BP ≤ 150 mmHg and diastolic BP ≤ 90 mmHg), ***if anti-hypertensive medication(s) are needed.***

Note: Patients who are not eligible based on the AC→WP regimen BP criteria but who meet the TC regimen BP criteria are eligible for B-47, if the intended chemotherapy regimen is changed to TC.

4.3.14 Active hepatitis B or hepatitis C with abnormal liver function tests.

4.3.15 Intrinsic lung disease resulting in dyspnea.

4.3.16 Poorly controlled diabetes mellitus.

4.3.17 Active infection or chronic infection requiring chronic suppressive antibiotics.

4.3.18 Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ grade 2, per the CTCAE v4.0.

4.3.19 Conditions that would prohibit administration of corticosteroids.

4.3.20 Chronic daily treatment with corticosteroids with a dose of ≥ 10 mg/day methylprednisolone equivalent (excluding inhaled steroids).

4.3.21 Known hypersensitivity to any of the study drugs or excipients, e.g., polysorbate 80 and Cremophor® EL.

4.3.22 Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing must be performed within 2 weeks prior to randomization according to institutional standards for women of childbearing potential.)***

4.3.23 Other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.

4.3.24 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

4.3.25 Use of any investigational product within 30 days prior to randomization.

5.0 CARDIAC SAFETY MONITORING

5.1 Timing of LVEF assessments

LVEF assessments are required at the timepoints listed on Table 6.

TABLE 6. Timing of LVEF assessments

For patients in Groups 1A and 1B (TC; AC→WP)	For patients in Group 2A (TC+H)	For patients in Group 2B (AC→WP+H→H)
• Baseline – within 90 days prior to randomization • At 12 months following randomization **for the first 800 patients randomized to Arm 1 (chemotherapy regimens A and B)**	• Baseline – within 90 days prior to randomization • At 3 months following randomization (after cycle 4) • At 6 months following randomization • At 9 months following randomization • At 12 months following randomization	• Baseline – within 90 days prior to randomization • At 3 months following randomization (10–21 days after the last dose of AC [before WP+H begins]) • At 6 months following randomization • At 9 months following randomization • At 12 months following randomization

5.2 Important LVEF assessment guidelines

- ***2-D echocardiogram is the preferred method for assessment of LVEF.*** However, LVEF assessment by MUGA scan is permitted.
- ***All LVEF assessments should be performed by the same method*** (either 2-D echocardiogram or MUGA scan) that was performed at baseline.
- Investigators are strongly urged to schedule the LVEF assessment at the same cardiac imaging facility that performed the patient's baseline LVEF assessment.
- If trastuzumab is discontinued for any reason, protocol-mandated LVEF assessments should continue to be obtained. (Exception: LVEF assessments are not required following a documented invasive breast cancer recurrence, invasive contralateral breast cancer, or second nonbreast primary cancer excluding squamous or basal cell skin cancers or new in situ carcinomas of any site.)

5.3 Reporting LVEF assessments

- The LVEF value must be reported on the LVEF Assessment report form (Form LVA) as a numerical value that is a whole number.
  - If the facility performing the assessment has not reported the LVEF as a whole number, decimals reported as ≥ 5 should be rounded up and decimals reported as < 5 should be rounded down. For example, an LVEF of 54.5% will be rounded up and reported as 55%; an LVEF of 54.4% will be rounded down and reported as 54%.
  - If the facility performing the assessment will only report the LVEF as a range, the mean (average) of the values used for the range should be calculated so that a single numerical value can be reported.

- During therapy and until 30 days after the last dose of study therapy (either as part of required CTEP-AERS reports or as part of routine AE reporting), ≥ grade 2 decreases in LVEF must also be reported as an AE (see "Ejection Fraction Decreased" in the Investigations section of the CTCAE v4.0).
- Submission of Form LVA with the echocardiogram scan or MUGA scan report to the NRG Oncology SDMC (see Information Resources on page 11) is required **within 21 days after all LVEF assessments**. For all patients, regardless of treatment assignment, Form LVA must be submitted as follows:
  - Following required LVEF assessments at the protocol-specified time points (see Section 5.1)
  - If an LVEF assessment is performed because the patient has signs or symptoms of CHF, i.e., ≥ grade 3 left ventricular systolic dysfunction or ≥ grade 2 heart failure per the CTCAE v4.0, at any time through 10 years following randomization (see Section 5.5)

5.4 Reporting cardiac events

The cardiac events listed in Sections 5.4.1 and 5.4.2, as defined in the CTCAE v4.0, must be reported in an expedited manner via CTEP-AERS **from the time of the first dose of study therapy (chemotherapy with or without trastuzumab) until 2 years following randomization**. The Cardiac Report form (Form CR) must be submitted to the NRG Oncology SDMC within 21 days of learning of the cardiac events listed. Also submit Form LVA and the echocardiogram or MUGA scan report, if applicable. (Refer to Section 13.3 for instructions regarding expedited reporting.)

5.4.1 *Protocol-defined cardiac events*

- ≥ grade 2 heart failure
- ≥ grade 3 left ventricular systolic dysfunction
- Definite cardiac death defined as any grade 5 AE included in the Cardiac Disorders section of the CTCAE v4.0
- Sudden death NOS as defined in the General Disorders section of the CTCAE v4.0

5.4.2 *Other cardiac events*

- ≥ grade 3 acute coronary syndrome
- ≥ grade 3 myocardial infarction

5.5 Reporting selected late cardiac events

For the first 2 years following randomization, selected cardiac events will be reported via CTEP-AERS and on Form CR as described in Section 5.4. **Beginning at Year 3 and continuing through Year 10**, the following selected late cardiac events, as defined in the Cardiac Disorders section of the CTCAE v4.0, will be reported on the B-47 follow-up form and Form CR:

- ≥ grade 3 acute coronary syndrome
- ≥ grade 2 heart failure
- ≥ grade 3 left ventricular systolic dysfunction
- ≥ grade 3 myocardial infarction

5.6 **Required cardiac event follow-up reporting**

A cardiac event follow-up form will be used to collect information regarding the resolution of **heart failure and left ventricular systolic dysfunction**, as well as the need for therapy to manage symptoms of CHF. After NRG Oncology reviews documentation related to the initial report of heart failure or left ventricular systolic dysfunction (reported via CTEP-AERS or on the B-47 follow-up form), the Program Coordinator will be notified whether or not submission of a cardiac event follow-up form will be required. When required, a cardiac event follow-up form will be submitted every 6 months for 2 years.

6.0 REQUIREMENTS FOR ENTRY, TREATMENT AND FOLLOW-UP

Note: Accrual closed on February 10, 2015, following achievement of the sample size goal.

Tests, exams, and other assessments required prior to randomization are listed on Table 7. Requirements during Year 1 are outlined on Table 8 for patients in Groups 1A and 1B and on Table 9 for patients in Groups 2A and 2B. Requirements for Years 2 through 10 are listed on Table 10 for patients in all treatment groups.

TABLE 7. Tests, exams, and other requirements prior to randomization

Required Assessments	Prior to Randomization	
Determination of local pathology department's policy re: submission of tumor samples (see Section 4.1)	X	
Consent form signed by the patient	X	
Determination of hormone receptor status (see Section 4.2.13)	X	
HER2 analysis (see Sections 4.2.7 and 4.3.1)	X	
History & physical exam	X[a]	Within 4 weeks *(must be postoperative)*
Height & weight	X	
Performance status (see Appendix A)	X	
Menstrual history	X[b]	
Menopausal status (see Appendix C)	X[c]	
Assessment of BP and BP medications	X	
Assessment of concomitant medications	X	
Assessment of alcohol and tobacco use and comorbid conditions (questionnaire completed by the patient)	X[d]	
CBC/differential/platelet count	X	Within 6 weeks (must be most recent *postoperative* test results)
Total bilirubin/alkaline phosphatase/AST[e]	X	
Serum creatinine	X	
Pregnancy test	X[f]	Within 2 weeks
2-D echocardiogram (or MUGA scan)	X[g]	Within 90 days
ECG	X	
Chest imaging (chest CT scan or chest x-ray)	X[h,i]	
Liver imaging	X[i,j]	Within 90 days *(if required)*
Bone nuclear imaging	X[i,k]	
Bilateral breast imaging	X[l]	Within 180 days

(Table 7 is continued on the next page.)

TABLE 7. Tests, exams, and other requirements prior to randomization *(continued)*

a	The exam can be performed by a physician or other healthcare professional.
b	The baseline menstrual history assessment will identify women who will be included in the menstrual history study after randomization.
c	An estradiol level may be required. Refer to the criteria in Appendix C.
d	Questionnaire must be completed after signing the B-47 consent form.
e	ALT may be substituted for AST if required by the institution's standard practice.
f	For women of childbearing potential: Pregnancy testing should be performed according to institutional standards.
g	***2-D echocardiogram is the preferred method for assessment of LVEF.*** However, LVEF assessment by MUGA scan is permitted.
h	PET scans and PET-CT scans are permitted as an alternative to CT scans of the chest and chest x-ray.
i	Canadian investigators: Refer to Section 15.7 for regulatory requirements related to PET scans.
j	Liver imaging is required if alkaline phosphatase or AST is > ULN. Acceptable methods of liver imaging include CT, MRI, PET-CT, and PET scans to rule out metastatic disease.
k	Bone nuclear imaging is required if alkaline phosphatase is > ULN or if the patient has unexplained bone pain. PET scan or PET-CT scan is permitted as a substitute for a bone scan.
l	MRI is permitted before entry as a substitute for a mammogram (ultrasound is not). Imaging will be unilateral for patients who have had mastectomy with or without reconstruction.

TABLE 8. Tests, exams, and other requirements during therapy and through Year 1 **for Groups 1A and 1B**

Required assessments *(see footnote **a**)*	**After randomization**	**Within 3 days before each cycle** *(beginning with Cycle 2)*	**4 weeks after last chemotherapy dose**	**From end of chemotherapy through Year 1**
History & physical exam**b**		X	X	X (every 6 months)
Adverse event assessment		X**c**	X**c**	X**c**
Weight		X		X (12 months from randomization)
Height				
Assessment of concomitant medications				
Assessment of alcohol/tobacco use and comorbid conditions (questionnaire completed by the patient)				
CBC/differential/platelets		X (For WP, prior to doses 1, 4, 7, and 10)		
Serum creatinine				
Total bilirubin/alk phos/AST**d**				
2-D echocardiogram (or MUGA scan)**e**				X (12 months from randomization)
Bilateral mammogram			X (every 12 months)**f**	
Submission of tumor sample(s)	X**g**			
Menstrual history assessment		X**h** (about 3 months from randomization)**i**	X**h** (6 months from randomization)	X**h** (12 months from randomization)
Submission of blood samples for patients in the MH study population	X**j** (before therapy begins)	X**j** (about 3 months from randomization)**i**	X**j** (6 months from randomization)	X**j** (12 months from randomization)
Submission of blood samples for all consenting B-47 patients	X**k** (before therapy begins)			X**k** (12 months from randomization)

(Table 8 is continued on the next page.)

TABLE 8. Tests, exams, and other requirements during therapy and through Year 1 **for Groups 1A and 1B** *(continued)*

a	H&P, bloodwork, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.
b	Updated H&P with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations.
c	See instructions in Sections 5.4, 5.6, and Table 32 in Section 13.3 for reporting cardiac events; also see Section 13.4.2 for instructions regarding submission of Form TRTAE.
d	ALT may be substituted for AST if required by the institution's standard practice.
e	***Only required for the first 800 patients randomized to Arm 1.*** 2-D echo is the preferred method of LVEF assessment, but MUGA scan is permitted. If possible, all LVEF assessments should be performed by the same method at the same facility.
f	***Mammogram*** is required; unilateral for patients who have had mastectomy with or without reconstruction. First mammogram will be 1 year from the most recent mammogram (or MRI) performed prior to randomization and then every 12 months.
g	Submission of tumor sample(s) is ***required for all patients*** within 90 days following randomization; see Information Resources, Section 7.1, B-47 Pathology and Correlative Science Instructions.
h	Only for patients who, at time of randomization, were determined to be in the MH study population (see Section 8.2). Assessments are required even if the patient has not agreed to blood sample submission.
i	Before Cycle 5 for patients receiving TC; before WP for patients receiving AC→WP.
j	These blood samples are ***only required for patients who, at time of randomization, were determined to be in the MH study population and who have agreed to optional blood sample collections*** when signing the consent form (see Information Resources, Sections 7.1 and 8.2.6, and the B-47 Pathology and Correlative Science Instructions).
k	These blood samples are ***only required for patients who have agreed to optional sample collections*** when signing the consent form (see Information Resources, Sections 7.1, 8.3.5, and the B-47 Pathology and Correlative Science Instructions).

NOTE*: Tests, exams, assessments, and blood sample submissions* ***are not required*** *following a documented invasive breast cancer recurrence, invasive contralateral breast cancer, or second nonbreast primary cancer excluding squamous or basal cell skin cancers or new in situ carcinomas of any site. Follow-up for subsequent cancer events and for survival continues to be required every 6 months until year 6 and then every 12 months through Year 10. (See Section 13.0 for adverse event reporting requirements.)*

TABLE 9. Tests, exams, and other requirements during therapy and through Year 1 **for Groups 2A and 2B**

Required assessments *(see footnote **a**)*	**After randomization**	**Within 3 days before each chemotherapy cycle** *(beginning with Cycle 2)*	**2-4 weeks after last chemotherapy dose**	**Every 9 weeks during trastuzumab** *(after completion of chemotherapy)*	**At 12 months from randomization**
History & physical exam[b]		X	X	X[c]	X
Adverse event assessment		X[d]	X[d]	X[d]	X[e]
Weight		X		X	X
Height					
Assessment of concomitant meds					
Assessment of alcohol/tobacco use and comorbid conditions (questionnaire completed by patient)					
CBC/differential/platelets		X (For WP, prior to doses 1, 4, 7, and 10)			
Serum creatinine					
Total bilirubin/alk phos/AST[f]					
2-D echocardiogram (or MUGA scan)[g]		X[h] (3 months from randomization)	X (6 months from randomization)	X (9 months from randomization)	X
Bilateral mammogram			X (every 12 months)[i]		
Submission of tumor sample(s)	X[j]				
Menstrual history assessment		X[k] (about 3 months from randomization)[l]	X[k] (6 months from randomization)		X[k]
Submission of blood samples for patients in the MH study population	X[m] (before therapy begins)	X[m] (about 3 months from randomization)[l]	X[m] (6 months from randomization)		X[m]
Submission of blood samples for all consenting B-47 patients	X[n] (before therapy begins)				X[n]

(Table 9 is continued on the next page.)

TABLE 9. Tests, exams, and other requirements during therapy and through Year 1 **for Groups 2A and 2B** *(continued)*

a	H&P, bloodwork, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.
b	Updated H&P with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations.
c	Assessment sufficient for identification of AEs is required every 9 weeks; more comprehensive assessment should be performed every 12 weeks.
d	See instructions for reporting cardiac events in Sections 5.4, 5.6, and Table 32 in Section 13.3; also see Section 13.4.2 for instructions regarding submission of Form TRTAE.
e	AE assessment must be performed 30 days after the last dose of trastuzumab; this assessment may be based on patient exam or phone assessment.
f	ALT may be substituted for AST if required by the institution's standard practice.
g	***Required for all patients randomized to Arm 2.*** 2-D echo is the preferred method of LVEF assessment, but MUGA scan is permitted. If possible, all LVEF assessments should be performed by the same method at the same facility.
h	This LVEF assessment must be 10–21 days after the last AC dose (before beginning WP+H) for patients in Groups 2B and after Cycle 4 for patients in Group 2A (TC+H). See Table 6.
i	***Mammogram*** is required; unilateral for patients who have had mastectomy with or without reconstruction. First mammogram will be 1 year from the most recent mammogram (or MRI) performed prior to randomization and then every 12 months.
j	Submission of tumor sample(s) is ***required for all patients*** within 90 days following randomization; see Information Resources, Section 7.1, and B-47 Pathology and Correlative Science Instructions.
k	Only for patients who, at time of randomization, were determined to be in the MH study population (see Section 8.2). Assessments are required even if the patient has not agreed to blood sample submission.
l	Before Cycle 5 for patients receiving TC; before WP for patients receiving AC→WP.
m	Blood samples are ***only required for patients who, at time of randomization, were determined to be in the MH study population and who have agreed to optional blood sample collections*** when signing the consent form (see Information Resources, Sections 7.1 and 8.2.6, and the B-47 Pathology and Correlative Science Instructions).
n	Blood samples are ***only required for patients who have agreed to optional sample collections*** when signing the consent form (see Information Resources, Sections 7.1, 8.3.5, and the B-47 Pathology and Correlative Science Instructions).

***NOTE**: Tests, exams, assessments, and blood sample submissions **are not required** following a documented invasive breast cancer recurrence, invasive contralateral breast cancer, or second nonbreast primary cancer excluding squamous or basal cell skin cancers or new in situ carcinomas of any site. Follow-up for subsequent cancer events and for survival continues to be required every 6 months until year 6 and then every 12 months through Year 10. (See Section 13.0 for adverse event reporting requirements.)*

TABLE 10. Tests, exams, and other requirements during year 2 through year 10 for patients in all treatment groups

Required assessments *(see footnote **a**)*	**Years 2 through 5** *(from randomization)*	**Years 6 through 10** *(from randomization)*
History & physical exam**b**	X (every 6 months)	X (every 12 months)
Adverse event assessment	X**c** (every 6 months for selected late cardiac AEs)	X**c** (every 12 months for selected late cardiac AEs)
Weight	X (24, 36, 48, and 60 months from randomization)	
Height		
Assessment of concomitant medications		
Assessment of alcohol/tobacco use and comorbid medical conditions (questionnaire completed by patient)		
Menstrual history assessment	X**d** (18, 24, 30, and 36 months from randomization)	
Submission of blood samples for patients in the MH study population**e**	X**e** (18 and 24 months from randomization)	
Bilateral mammogram	X**f** (every 12 months)	X**f** (every 12 months)

a H&P, bloodwork, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.
b Updated H&P with exams (by physician or other healthcare professional) appropriate for follow-up evaluations.
c See instructions in Sections 5.4, 5.5, 5.6, Table 31 or Table 32 in Section 13.3, and 13.5 for reporting cardiac events including selected late cardiac events.
d Only for patients who, at time of randomization, were determined to be in the MH study population (see Section 8.2). Assessments are required even if the patient has not agreed to blood sample submission.
e Blood samples are ***only required for patients who, at time of randomization, were determined to be in the MH study population and who have agreed to optional blood sample collections*** when signing the consent form (see Information Resources, Sections 7.1 and 8.2.6, and the B-47 Pathology and Correlative Science Instructions).
f ***Mammogram*** is required; unilateral for patients who have had mastectomy with or without reconstruction.

***NOTE**: Tests, exams, assessments, and blood sample submissions **are not required** following a documented invasive breast cancer recurrence, invasive contralateral breast cancer, or second nonbreast primary cancer excluding squamous or basal cell skin cancers or new in situ carcinomas of any site. Follow-up for subsequent cancer events and for survival continues to be required every 6 months until year 6 and then every 12 months through Year 10. (See Section 13.0 for adverse event reporting requirements and Sections 8.2.6 and 8.3.5 for **blood sample submission requirements**.)*

7.0 PATHOLOGY AND CORRELATIVE SCIENCE STUDIES

7.1 Overview of requirements

Tumor sample submission is a protocol requirement and therefore mandatory for participation in the study (see Table 11 for specific requirements). ***By signing the B-47 consent form, the patient has agreed to tumor sample submission.*** Submission of the blood samples is only required for patients who agreed to optional blood sample collections in the B-47 consent form.

TABLE 11. Summary of B-47 tumor and blood sample submission requirements

Specimen requirements	After randomization before therapy begins	Within 90 days after randomization	At 3, 6, 12, 18, and 24 months after randomization
Tumor blocks **required for all patients**: – At least one paraffin block from the primary tumor (preferably more than one block) – one block from at least one positive lymph node (if applicable)		Yes[a,b]	
Diagnostic H&E slides	No	No	No
Blood samples for all B-47 consenting patients[c]	Yes[c]	No	Yes[c] (at 12 months only)
Blood samples for patients in the MH study population[d]	Yes[d]	No	Yes[d]

a If possible, the submitted block should be the one used for original HER2 testing and should contain the largest tumor volume.

b If the pathology department refuses to provide a block for research purposes, refer to the B-47 Pathology and Correlative Science Instructions for alternative sample submission instructions.

c Blood samples are ***only required for patients who have agreed to optional blood sample collections*** when signing the B-47 consent form (see Information Resources and Sections 7.1and 8.3.5).

d Blood samples are ***only required for patients who, at time of randomization, were determined to be in the menstrual history study population and who have agreed to optional blood sample collections*** when signing the B-47 consent form (see Information Resources and Sections 7.1 and *8.2.6*).

Note: Refer to the Members' Area of the NSABP Web site for the B-47 Pathology and Correlative Science Instructions.

7.2 Use of specimens

The tumor and blood samples collected in this study will be used for studies specified in the B-47 protocol and for studies to be conducted in the future related to the purposes of the B-47 study and not currently described in the protocol document.

Specific aims include the following: developing predictive tests for degree of benefit from trastuzumab; developing prognostic tests for patients treated with chemotherapy alone or chemotherapy plus trastuzumab; and testing the role of ADCC as a mechanism of action of trastuzumab. ***The procured specimens, including DNA samples derived from them, will not be***

used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or an anonymization process is used. Results of the correlative science studies will not be reported to the patient or her physician and will not have any bearing on her treatment.

7.3 Specimen submission and identification procedures

Refer to Information Resources on page 11 and to the B-47 Pathology Instructions in the Members' Area of the NSABP Web site for details regarding submission of specimens.

7.3.1 *Blocks*

Submitted blocks are initially shipped to and logged into the database at the NRG Oncology SDMC. These samples are then stripped of patient identifiers except the B-47 Patient ID number and forwarded to the NRG Oncology Biospecimen Bank-Pittsburgh where they are assigned a code number for further processing and study.

7.3.2 *Blood samples for B-47 correlative science studies*

The blood specimens are to be submitted to the NRG Oncology Serum Bank at the Baylor College of Medicine where they are logged into the database and assigned a specimen number. The samples are stripped of patient identifiers, except the B-47 Patient ID number, and are processed and stored until assays are performed to examine the role of a polymorphism of the Fcγ Receptor as a predictor of trastuzumab benefit. The samples collected at the 12-month time point will be used to identify immunological parameters that may correlate with treatment outcomes resulting from the addition of trastuzumab therapy. Additionally, these blood samples will also be used for the B-47 Host Factors sub-study (see Section 8.3.5).

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9.0 TREATMENT REGIMEN

9.1 Chemotherapy regimen for Group 1A (TC [docetaxel and cyclophosphamide])

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is at the investigator's discretion.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the investigator's discretion or per practice standards.

TABLE 13. Treatment regimen for **Group 1A (TC)**

Drug	Dose	Dosing Interval	Planned Duration
Docetaxel (T)	75 mg/m^2 IV over 60 minutes *(See footnote below for premedication instructions)*	Day 1 every 3 weeks	Cycles 1-6
Cyclophosphamide (C)	600 mg/m^2 IV over 30 minutes		
All patients should receive premedications as follows before each docetaxel dose: • Dexamethasone 8 mg by mouth twice daily the day before and the day of chemotherapy is recommended. At the physician's discretion, dexamethasone may be continued on the day after chemotherapy. An equivalent dose of other corticosteroids may be substituted (dexamethasone 8 mg = methylprednisolone 40 mg = prednisone 50 mg = prednisolone 50 mg). • Administration of IV dexamethasone (dose at the investigator's discretion) as a substitute for oral dexamethasone prior to chemotherapy is at the investigator's discretion. • At the investigator's discretion, other non-steroidal premedications, e.g., diphenhydramine hydrochloride 50 mg IV and H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) may be given in addition to dexamethasone.			

9.2 Chemotherapy and trastuzumab regimen for Group 2A (TC+H→H [docetaxel plus cyclophosphamide plus trastuzumab followed by trastuzumab])

- Chemotherapy and trastuzumab should begin within 2 weeks following randomization.
- ***Central venous access is recommended.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the treating physician's discretion or per practice standards.

TABLE 14. Treatment regimen for **Group 2A (TC+H→H)**

Drug	Dose	Dosing Interval	Planned Duration
Docetaxel (T)	75 mg/m^2 IV over 60 minutes *(See footnote **a** for premedication instructions)*	Day 1 every 3 weeks	Cycles 1-6
Cyclophosphamide (C)	600 mg/m^2 IV over 30 minutes		
Trastuzumab (H) *See footnote **b** re: LVEF requirements*	*First dose:* 8 mg/kg IV over 90 minutes[c]	Day 1 of Cycle 1 only	
	Subsequent doses during TC: 6 mg/kg IV over 30-60 minutes[c]	Day 1 every 3 weeks	Cycles 2-6
Continue trastuzumab 3 weeks after the last dose of chemotherapy/trastuzumab			
Trastuzumab (H) *See footnote **b** re: LVEF requirements*	6 mg/kg IV over 30-90 minutes[c] *(Use of premedications is at the investigator's discretion)*	Every 3 weeks	Until 1 year following first trastuzumab dose regardless of any missed doses[d]

a All patients should receive premedications as follows before each docetaxel dose:

- Dexamethasone 8 mg by mouth twice daily the day before and the day of chemotherapy is recommended. At the physician's discretion, dexamethasone may be continued on the day after chemotherapy. An equivalent dose of other corticosteroids may be substituted (dexamethasone 8 mg = methylprednisolone 40 mg = prednisone 50 mg = prednisolone 50 mg).
- Administration of IV dexamethasone (dose at the investigator's discretion) as a substitute for oral dexamethasone prior to chemotherapy is at the investigator's discretion.
- At the physician's discretion, other non-steroidal premedications, e.g., diphenhydramine hydrochloride 50 mg IV and H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) may be given in addition to dexamethasone.

b See Section 11.3 (including Table 28) for LVEF requirements for the continuation of trastuzumab.

c See Table 29 for instructions regarding trastuzumab infusion-related reactions, allergic reactions, and anaphylaxis.

d One year of therapy is defined as 51 weeks and includes the period of time trastuzumab is given with chemotherapy (18 weeks) + the time during which trastuzumab is given alone (33 weeks). For patients who have received all of the planned therapy on schedule, 17 doses of trastuzumab will be administered.

9.3 Treatment regimen for Group 1B (AC→WP [doxorubicin plus cyclophosphamide followed by weekly paclitaxel])

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is at the investigator's discretion.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and the order of drug administration may be altered at the treating physician's discretion or per practice standards.

TABLE 15. Treatment regimen for **Group 1B (AC→WP)**

Drug	Dose	Dosing Interval	Planned Duration
Doxorubicin (A)	60 mg/m^2 IV over 15 minutes	Day 1 every 3 weeks **OR** Day 1 every 2 weeks (dose-dense)**a**	Cycles 1-4
Cyclophosphamide (C)	600 mg/m^2 IV over 30 minutes		
Initiate 3 weeks after the last dose of AC (see footnote b)			
Paclitaxel (WP)	80 mg/m^2 IV over 60 minutes *See footnote **c** for premedications*	Weekly	12 doses**d**

a Choice of AC schedule (every 3 weeks or every 2 weeks [dose-dense]) is at the investigator's discretion. ***If the dose-dense schedule is used, primary prophylaxis with G-CSF is required during AC*** (see Section 9.7.1 for instructions).

b If the dose-dense schedule is used for AC, paclitaxel will be initiated 2-3 weeks after the last dose of AC.

c All patients should receive premedications as follows before each paclitaxel dose:
- Dexamethasone 10 mg IV, completed 30 minutes before each paclitaxel administration. (At the investigator's discretion, dexamethasone may be tapered during the paclitaxel cycles.)
- Diphenhydramine hydrochloride 50 mg IV and an H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) before each paclitaxel administration.

d Paclitaxel therapy must stop 16 weeks after the first dose of paclitaxel. If medical or non-medical treatment delays occur during paclitaxel therapy, administer as many of the remaining doses as possible by 16 weeks.

9.4 Treatment regimen for Group 2B (AC→WP+H→H [doxorubicin plus cyclophosphamide followed by weekly paclitaxel plus trastuzumab followed by trastuzumab])

- Chemotherapy should begin within 2 weeks following randomization.
- ***Central venous access is recommended.*** If prophylactic coumadin (or equivalent) is used, the dose should not exceed 1 mg/day.
- Infusion times and order of drug administration may be altered at the treating physician's discretion or per practice standards.

TABLE 16. Treatment regimen for **Group 2B (AC→WP+H→H)**

Drug	Dose	Dosing Interval	Planned Duration
Doxorubicin (A)	60 mg/m2 IV over 15 minutes	Day 1 every 3 weeks **OR** Day 1 every 2 weeks (dose-dense)[a]	Cycles 1-4
Cyclophosphamide (C)	600 mg/m2 IV over 30 minutes		
Initiate 3 weeks after the last dose of AC (see footnote b)			
Paclitaxel (WP)	80 mg/m2 IV over 60 minutes *See footnote **c** for premedications*	Weekly	12 doses[d]
Trastuzumab (H) *See footnote **e** re: LVEF requirements*	*First dose:* 4 mg/kg IV over 90 minutes[f]	Day 1 only	
	Subsequent doses during WP: 2 mg/kg IV over 30 minutes[f]	Weekly	11 doses[g]
Continue trastuzumab 1 week after the last dose of WP/trastuzumab			
Trastuzumab (H) *See footnote **h** re: LVEF requirements*	6 mg/kg IV over 30–90 minutes[f] *(Use of premedications is at the investigator's discretion)*	Every 3 weeks	Until 1 year following first trastuzumab dose regardless of any missed doses[i]

a Choice of AC schedule (every 3 weeks or every 2 weeks [dose-dense]) is at the investigator's discretion. ***If the dose-dense schedule is used, primary prophylaxis with G-CSF is required during AC*** (see Section 9.7.1 for instructions).

b If the dose-dense schedule is used for AC, paclitaxel will be initiated 2–3 weeks after the last dose of AC.

c All patients should receive premedications as follows before each paclitaxel dose:
- Dexamethasone 10 mg IV, completed 30 minutes before each paclitaxel administration. (At the investigator's discretion, dexamethasone may be tapered during the paclitaxel cycles.)
- Diphenhydramine hydrochloride 50 mg IV and an H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) before each paclitaxel administration.

d Paclitaxel therapy must stop 16 weeks after the first dose of paclitaxel. If medical or non-medical treatment delays occur during paclitaxel therapy, administer as many of the remaining doses as possible by 16 weeks.

e ***The post-AC LVEF must meet Section 9.6 (Table 17) criteria before trastuzumab therapy begins.***

f See Table 29 for instructions regarding trastuzumab infusion-related reactions, allergic reactions, and anaphylaxis.

g If paclitaxel is held, trastuzumab should be continued (see Section 11.2).

h See Section 11.3 (including Table 28) for LVEF requirements for the continuation of trastuzumab.

i One year of therapy is defined as 51-52 weeks and includes the period of time trastuzumab is given with weekly paclitaxel (12–16 weeks) + the time during which trastuzumab is given alone (36–40 weeks depending on the duration of the weekly paclitaxel therapy). ***For patients who have received all of the planned therapy (without delays), 12 doses of trastuzumab will be administered weekly followed by a maximum of 13 doses administered every 3 weeks.***

9.5 Dose determination

9.5.1 *Calculation of BSA, chemotherapy doses, and trastuzumab dose*

- Recommended chemotherapy and trastuzumab doses will be provided by NRG Oncology at the time of study entry.
- Recalculation of BSA and drug doses is ***required*** if the patient has a 10% or greater change in weight from baseline or, if the dose has already been adjusted due to weight change, from the weight at the time of the most recent dose adjustment. At the physician's discretion, the BSA and drug doses may be recalculated before each treatment.

9.5.2 *Rounding doses*

Rounding of drug doses is optional. If the treating physician decides to round the dose(s), follow these guidelines. (These also apply to dose modifications.)

- ***Cyclophosphamid***e (600 mg/m^2 IV)

  Doses should be rounded to the nearest 20 mg.

- ***Docetaxel*** (75 mg/m^2 IV)

  Doses should be rounded to the nearest 5 mg.

- ***Doxorubicin*** (60 mg/m^2 IV)

  Doxorubicin should be rounded to the nearest 1 mg.

- ***Paclitaxel*** (80 mg/m^2 IV)

  Paclitaxel should be rounded to the nearest 5 mg.

- ***Trastuzumab*** (see Table 14 and Table 16 for dosing)

  Trastuzumab should be rounded to the nearest 20 mg.

9.6 Cardiac safety criteria for initiation of trastuzumab therapy following AC (for Group 2B patients only)

See Section 9.6.2 for asymptomatic decrease in LVEF.

9.6.1 *Patients with cardiac AEs during AC*

If the patient develops any of the following cardiac AEs during AC, protocol therapy should be discontinued and further therapy is at the investigator's discretion. ***Initiation of trastuzumab is prohibited.***

- Any ≥ grade 2 cardiac AE listed in Appendix D.
- Any ≥ grade 3 AE listed in the Cardiac Disorders section of the CTEP Active Version of the CTCAE.

9.6.2 *Patients with asymptomatic decrease in LVEF*

For patients who do not develop symptoms related to LV dysfunction or other cardiac AEs as described in Section 9.6.1, initiation of trastuzumab therapy for Group 2B patients will depend on the absolute LVEF value and absolute change in percentage points between the baseline LVEF and the **LVEF assessed 10-21 days after the last AC dose** as outlined on Table 17.

TABLE 17. LVEF requirements for initiation of trastuzumab therapy after AC **(Group 2B only)**

LVEF assessed 10-21 days after last AC dose	**Change in LVEF percentage points from baseline (see footnote a)**		
	Increase or no change	**Decrease of < 10 percentage points**	**Decrease of ≥ 10 percentage points**
≥ 55%	Initiate trastuzumab therapy		
50-54%	N/A	Initiate trastuzumab therapy	Initiate trastuzumab therapy and repeat echo/MUGA in **6** weeks[b]
≤ 49%	N/A	Do NOT initiate trastuzumab therapy; Initiate paclitaxel per protocol[c]	

a The baseline LVEF is the LVEF measured prior to randomization.

b If repeat echo/MUGA was required, the LVEF value for the 2nd assessment must meet Table 17 criteria for trastuzumab to be initiated.

c Patient follow-up (including LVEF assessments) should continue as per protocol instructions on Table 9.

9.7 Supportive therapy

9.7.1 *G-CSF*

- If the dose-dense schedule is followed for AC, primary prophylaxis with G-CSF is required. For all other chemotherapy regimens, use of G-CSF as primary prophylaxis is at the investigator's discretion. If utilized, it should be administered according to the package insert for the agent used.
- If G-CSF support is required during TC therapy (see Table 19) or AC therapy for the every-3-week schedule (see Table 23), either pegfilgrastim or filgrastim may be used at the investigator's discretion. If G-CSF support is required during weekly paclitaxel therapy (see Table 25), filgrastim ***must*** be used.
- Do not administer G-CSF within 24 hours of chemotherapy.
- If required by institutional standards, GM-CSF may be administered as an alternative to G-CSF.

9.7.2 ***Erythropoietin***

Use of an erythropoiesis-stimulating agent is not permitted. (See Section 10.2 for instructions regarding ≥ grade 3 anemia.)

9.7.3 ***Antiemetic therapy***

Antiemetic therapy should be administered according to National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) clinical practice guidelines.

9.7.4 ***Management of docetaxel-related edema***

Suggested interventions include:

- Hydrochlorothiazide/triamterene (Dyazide®) 1 capsule by mouth daily; dose can be increased to twice daily.
- Furosemide (Lasix®) 40 mg by mouth daily if edema progresses despite Dyazide (or equivalent) therapy. Potassium supplementation should be given as needed.

9.8 Adjuvant radiation therapy

Choice of RT, treatment fields, and treatment schedule will be at the discretion of the radiation oncologist.

9.8.1 ***Whole breast irradiation (WBI) following breast conserving surgery***

WBI should begin within 6 weeks following the last dose of chemotherapy and will overlap with the administration of trastuzumab. Regional nodal irradiation is at the radiation oncologist's discretion.

9.8.2 ***Partial breast irradiation (PBI) following breast conserving surgery***

PBI utilizing 3-D conformal RT or brachytherapy is permitted **only if RT is completed on or before the date of randomization**.

9.8.3 ***Post-mastectomy RT***

RT is at the radiation oncologist's discretion.

9.9 Adjuvant endocrine therapy

Patients with ER-positive and/or PgR-positive tumors should receive a minimum of 5 years of endocrine therapy.

- Adjuvant endocrine therapy should be initiated 3–6 weeks following the completion of chemotherapy and will overlap with the administration of trastuzumab. *At the physician's discretion, initiation may be delayed until after completion of RT but should be initiated by 12 weeks following completion of chemotherapy.*
- LHRH agonist/antagonists (e.g., Lupron® and Zoladex®) or ovarian ablation by surgery or RT are permitted for premenopausal patients.
- Adjuvant endocrine therapy should be administered according to the current ASCO guidelines. However, selection of endocrine therapy will be at the physician's discretion. The dose and schedule of endocrine therapy should be consistent with the drug package insert.

9.10 Prohibited therapies

The following types of treatment, in addition to any cancer therapy other than the therapy specified in this protocol, are prohibited until the time of diagnosis of the first breast cancer recurrence or diagnosis of a second primary malignancy.

9.10.1 *Chemotherapy*

Administration of chemotherapy other than the chemotherapy specified in this protocol is prohibited.

9.10.2 *Targeted therapy*

Administration of targeted therapy for malignancy (other than trastuzumab for Groups 2A and 2B patients) is prohibited.

9.10.3 *Radiation therapy*

Partial breast irradiation following randomization is prohibited (see Section 9.8.2).

9.11 Participation in other clinical trials

- Patients may participate in the NSABP B-39/RTOG 0413 Trial.
- If a B-47 patient is considering participation in another clinical trial (including supportive therapy trials), contact the NRG Oncology Clinical Coordinating Department (see Information Resources on page 11).

10.0 CHEMOTHERAPY TREATMENT MANAGEMENT

10.1 General instructions

- The CTCAE v4.0 must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- All doses must be based on the AE requiring the greatest modification.
- Chemotherapy doses that have been reduced may not be escalated.
- Unless specified otherwise in the treatment management sections/tables, chemotherapy should be held for at least 1 week until clinically significant AEs return to ≤ grade 1.

10.2 Management of anemia

Chemotherapy should not proceed with ≥ grade 3 anemia. Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. *Use of erythropoiesis-stimulating agents is prohibited.*

10.3 Treatment management for TC (Groups 1A and 2A)

- If a docetaxel-related hypersensitivity reaction occurs despite premedication, treatment as medically indicated will be instituted. For ≤ grade 3 allergic reaction or grade 3 anaphylaxis, continuation of docetaxel is at the investigator's discretion. Following a grade 4 allergic reaction or grade 4 anaphylaxis, docetaxel must be permanently discontinued.
- Docetaxel-related fluid retention will be treated as per the investigator's discretion. See Section 9.7.4 for management suggestions.
- If trastuzumab must be discontinued before completion of the scheduled TC cycles, the remaining TC doses should be administered.
- All dose modifications for TC are based on the dose level changes outlined in Table 18.
- See Table 20 for management of docetaxel-related neuropathy and Table 21 for docetaxel-related musculoskeletal pain. Instructions for management of all other TC toxicities are listed on Table 19.

TABLE 18. Dose levels for TC **(Groups 1A and 2A)**

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**
Docetaxel (T)	75	60	Discontinue
Cyclophosphamide (C)	600	500	Discontinue

TABLE 19. Treatment management for TC **(Groups 1A and 2A)**

Important table instructions:

- Dose modifications must be based on AEs that occurred during the cycle (column 2) ***and*** AEs present on the scheduled Day 1 for Cycles 2-6 (column 3). Refer to all sections/tables within Section 10.1–10.3 for additional instructions.
- Modifications for toxicities on this table apply to both docetaxel and cyclophosphamide (TC).
- Dose modifications must be based on the AE requiring the greatest modification.
- **NOTE:** If the docetaxel dose has been previously reduced for docetaxel-specific toxicities (see Table 20 and Table 21) and a subsequent toxicity requiring dose reduction of TC occurs, maintain docetaxel at the reduced dose level (-1) and decrease cyclophosphamide to dose level -1; ***or***, at the investigator's discretion, discontinue all study therapy. Further therapy is then at the investigator's discretion. (See Sections 11.1 and 11.2 for trastuzumab instructions for Group 2A patients.)

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grade 2 (1000-1199/mm^3), Grades 3, 4	Maintain dose	**ANC**: *Hold until ≥ 1200/mm^3. If recovery takes:* 1-3 wks – maintain dose and add G-CSF *If receiving G-CSF and recovery takes:* 1 wk – maintain dose; 2-3 wks - ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	**Platelets**: *Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2 to 3 wks - ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3.* ↓ one dose level
GI *(if related to chemotherapy)*: **Diarrhea** Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Mucositis - oral Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Vomiting *(despite antiemetics)* Grade 2	Maintain dose or ↓ one dose level	Maintain dose or ↓ one dose level
Grades 3, 4	↓ one dose level or D/C	D/C
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	↓ one dose level	*Hold until bilirubin returns to the **baseline grade*** *and AST and alk phos have returned to ≤ grade 1;*↓ one dose level
Grade 3	↓ one dose level or D/C	*Hold until bilirubin returns to the **baseline grade*** *and AST and alk phos have returned to ≤ grade 1;* ↓ one dose level or D/C
Grade 4	D/C	D/C

(Table 19 is continued on the next page.)

TABLE 19. Treatment management for TC **(Groups 1A and 2A)** *(continued)*

Infection or febrile neutropenia: Grade 2 (N/A for febrile neutropenia)	Maintain dose and add G-CSF prophylaxis for subsequent chemotherapy cycles if neutropenia was present.**c**	
Grade 3	Maintain dose and add G-CSF prophylaxis for subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level.	
Grade 4	Maintain dose and add G-CSF prophylaxis for subsequent chemotherapy cycles or D/C. If receiving prophylactic G-CSF, ↓ one dose level or D/C.	
Other clinically significant AEs:[d] Grade 2	Maintain dose or ↓ one dose level	
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C

a Resolved means that all clinically significant AEs are ≤ grade 1 (except neutrophils, which must be ≥ 1200/mm^3, and bilirubin, which must be ≤ the baseline grade) on Day 1 of the next scheduled cycle, i.e., treatment can be given without delay.

b Hold and check weekly. With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1. If toxicity has not resolved to ≤ grade 1 after 3 weeks of delay, discontinue TC (see Section 11.2 for trastuzumab instructions for Group 2A).

c If grade 2 criteria for infection include topical antibiotics or other local treatment, use of G-CSF is at the investigator's discretion.

d Determination of "clinically significant" AEs is at the discretion of the investigator.

TABLE 20. Treatment management for docetaxel-related neuropathy

Nervous System Disorders • Paresthesias • Peripheral sensory neuropathy	**1 – 7 Days Duration**	**Persistent for > 7 Days *or* Caused the Next Cycle to be Delayed**
Grade 1	Maintain docetaxel dose	
Grade 2	Maintain docetaxel dose**a**	Decrease docetaxel one dose level**b**
Grade 3	**First episode:** Decrease docetaxel one dose level**a** **Second episode:** Discontinue docetaxel	Discontinue docetaxel
Grade 4	Discontinue docetaxel	

a Must be resolved to ≤ grade 1 on Day 1 of the next cycle.

b Hold chemotherapy for ***persistent*** grade 2 neuropathy. When ≤ grade 1, resume treatment with dose modification for docetaxel (no dose reduction for cyclophosphamide). If grade 2 toxicity persists after 3 weeks of delay, discontinue docetaxel. (For patients in Group 2A, see Section 11.2 for instructions regarding trastuzumab.)

TABLE 21. Treatment management for **docetaxel-related** musculoskeletal pain

Note: The treatment management instructions in Table 21 apply to patients with **musculoskeletal pain not controlled by analgesics**. Use of narcotics and NSAIDs is encouraged to maintain the docetaxel dose if possible.

Musculoskeletal and Connective Tissue Disorders • Arthralgia • Myalgia	**1 – 7 Days Duration**	**Persistent for > 7 Days *or* Caused the Next Cycle to be Delayed**
Grade 1 *(despite analgesics)*	Maintain docetaxel dose	
Grade 2 *(despite analgesics)*	Maintain docetaxel dose	Maintain docetaxel dose or Decrease docetaxel one dose level*
Grade 3 *(despite analgesics)*	**First episode:** Decrease docetaxel one dose level **Second episode:** Discontinue docetaxel	**First episode:** Decrease docetaxel one dose level* or Discontinue docetaxel **Second episode**: Discontinue docetaxel
* Hold docetaxel for ***persistent*** grade 2 or 3 musculoskeletal pain. ***(Cyclophosphamide and trastuzumab should be continued while docetaxel is held.)*** When ≤ grade 1, resume treatment with dose modification. If grade 2 or grade 3 toxicity persists after 3 weeks of delay, discontinue docetaxel. (For patients in Group 2A, see Section 11.2 for instructions regarding trastuzumab.)		

10.4 Treatment management for AC (Groups 1B and 2B)

10.4.1 *Cardiac AEs during AC*

If the patient develops any of the following cardiac AEs during AC, study therapy should be discontinued and further therapy is at the investigator's discretion.

- Any ≥ grade 2 cardiac AE listed in Appendix D.
- Any ≥ grade 3 AE listed in the Cardiac Disorders section of the CTCAE v.4.0.

10.4.2 *Non-cardiac toxicity*

- If AC is discontinued due to non-cardiac toxicity, paclitaxel and, for Group 2B patients, trastuzumab should be initiated.
- If AEs occurring during dose-dense AC have resulted in treatment delays, the AC therapy should be converted to the every-3-week treatment schedule.
- All dose modifications for AC are based on Table 22 dose level changes. Instructions for management of non-cardiac AC toxicities are listed on Table 23. The dose levels on Table 22 and the instructions on Table 23 apply to both AC treatment schedules (every-3-weeks and every-2-weeks [dose-dense]).

TABLE 22. Dose levels for AC **(Groups 1B and 2B)**

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Doxorubicin (A)	60	50	40	Discontinue
Cyclophosphamide (C)	600	500	400	Discontinue

TABLE 23. Treatment management for **AC** (Groups 1B and 2B)

Important table instructions:

- Dose modifications must be based on AEs that occurred during the cycle (column 2) ***and*** AEs present on the scheduled Day 1 of Cycles 2-4 (column 3). Refer to other applicable instructions in Section 10.1, 10.2, and 10.4.
- All modifications in dose levels apply to both doxorubicin and cyclophosphamide (AC).
- Dose modifications must be based on the AE requiring the greatest modification.
- If the dose-dense schedule for AC is used, primary prophylaxis with G-CSF is required.

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Neutrophil count decreased: Grade 2 (1000-1199/mm^3), Grades 3, 4	Maintain dose	**ANC**: *Hold until ≥ 1200/mm^3. If recovery takes:* 1-3 wks – maintain dose and add G-CSF**c** *If receiving G-CSF and recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	**Platelets**: *Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3.* ↓ one dose level
GI (if related to chemotherapy): **Diarrhea** Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Mucositis - oral Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C
Vomiting *(despite antiemetics)* Grade 2	Maintain dose or ↓ one dose level	Maintain dose or ↓ one dose level
Grades 3, 4	↓ one dose level or D/C	D/C
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	↓ one dose level	*Hold until bilirubin returns to the **baseline grade*** *and AST and alk phos have returned to ≤ grade 1;* ↓ one dose level
Grade 3	↓ one dose level or D/C	*Hold until bilirubin returns to the **baseline grade*** *and AST and alk phos have returned to ≤ grade 1;* ↓ one dose level or D/C
Grade 4	D/C	D/C

(Table 23 is continued on the next page.)

TABLE 23. Treatment management for **AC** (Groups 1B and 2B) *(continued)*

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote **b**)
Infection or febrile neutropenia: Grade 2 (N/A for febrile neutropenia)	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy cycles if neutropenia was present.**d**	
Grade 3	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy cycles. If receiving prophylactic G-CSF, ↓ one dose level.	
Grade 4	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy cycles or D/C. If receiving prophylactic G-CSF, ↓ one dose level or D/C.	
Other clinically significant AEs:[e] Grade 2	Maintain dose or ↓ one dose level	
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C

a Resolved means that all clinically significant AEs are ≤ grade 1 (except neutrophils, which must be ≥ 1200/mm^3, and bilirubin, which must be ≤ the baseline grade) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1.*** (See Section 10.4.2 regarding dose-dense AC). If toxicity has not resolved after 3 weeks of delay, discontinue AC and proceed to paclitaxel (and trastuzumab for Group 2B).

c Pegfilgrastim, at a fixed dose of 6 mg SQ on Day 2, is preferred. Filgrastim, if used, should be administered according to the drug package insert.

d If grade 2 criteria for infection include topical antibiotics or other local treatment, use of G-CSF is at the investigator's discretion.

e Determination of "clinically significant" AEs is at the discretion of the investigator.

10.5 Treatment management for WP and WP+H (Groups 1B and 2B)

See Section 11.0 for trastuzumab (H) management (Group 2B).

10.5.1 *Treatment decisions when paclitaxel must be held or discontinued*

- Unless otherwise specified, paclitaxel that is held due to toxicity will not resume until the toxicity has resolved to ≤ grade 1.
- Weekly paclitaxel (WP) must be completed within 16 weeks. Any of the 12 doses remaining after 16 weeks following the first paclitaxel dose should not be administered.

10.5.2 ***Instructions for dose modifications and treatment delays during paclitaxel***

- Dose modifications for paclitaxel are based on the dose level changes outlined on Table 24.
- Dose modifications and instructions for management of neuropathy related to paclitaxel are outlined on Table 26.
- Dose modifications and instructions for management of musculoskeletal pain related to paclitaxel are outlined on Table 27.
- Dose modifications for other toxicities are outlined on Table 25.

TABLE 24. Dose levels for paclitaxel **(Groups 1B and 2B)**

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Weekly paclitaxel (WP)	80	60	45	Discontinue

TABLE 25. Treatment management for weekly paclitaxel **(Groups 1B and 2B)**

Important table instructions:

- Dose modifications must be based on AEs that occurred between treatments (column 2) ***and*** AEs present on the scheduled treatment day (column 3). Refer to all sections/tables within Sections 10.1, 10.2, and 10.5 for additional instructions.
- Dose modifications must be based on the AE requiring the greatest modification.

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred between treatments but DID NOT REQUIRE A DELAY IN TREATMENT (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN THE NEXT TREATMENT (See footnote **b**)
Neutrophil count decreased: Grades 3, 4	Maintain dose	**ANC**: *Hold until* ***≥ 1000/mm^3;*** maintain dose and add G-CSF**c** *If receiving G-CSF,* ↓ one dose level
Platelet count decreased: Grades 2, 3	Maintain dose	**Platelets**: *Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3* ↓ one dose level
GI (if related to chemotherapy): **Diarrhea** Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	↓ one dose level or D/C
Mucositis - oral Grade 2	Maintain dose	Maintain dose or ↓ one dose level
Grade 3	↓ one dose level	↓ one dose level
Grade 4	D/C	D/C
Vomiting *(despite antiemetics)* Grade 2	Maintain dose or ↓ one dose level	Maintain dose or ↓ one dose level
Grades 3, 4	↓ one dose level or D/C	D/C
Investigations (hepatic): **Bilirubin, AST, alk phos** Grade 2	↓ one dose level	*Hold until bilirubin returns to the* ***baseline grade*** *and AST and alk phos have returned to ≤grade 1;* ↓ one dose level
Grade 3	↓ one dose level or D/C	*Hold until bilirubin returns to the* ***baseline grade*** *and AST and alk phos have returned to ≤grade 1;* ↓ one dose level or D/C
Grade 4	D/C	D/C
Infection or febrile neutropenia: Grade 2 (N/A for febrile neutropenia)	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy cycles if neutropenia was present.**d**	
Grade 3	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy treatments. If receiving prophylactic G-CSF, ↓ one dose level.	
Grade 4	Maintain dose and add G-CSF**c** prophylaxis for subsequent chemotherapy treatments or D/C. If receiving prophylactic G-CSF, ↓ one dose level or D/C.	

(Table 25 is continued on the next page.)

TABLE 25. Treatment management for weekly paclitaxel **(Groups 1B and 2B)** *(continued)*

CTCAE v4.0 Adverse Event/Grade	Modifications for AEs that occurred between treatments but DID NOT REQUIRE A DELAY IN TREATMENT (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY IN THE NEXT TREATMENT (See footnote **b**)
Other clinically significant AEs:[e] Grade 2	Maintain dose or ↓ one dose level	
Grade 3	↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or D/C	D/C

a ***Treatment may not proceed until clinically significant AEs are ≤grade 1*** (except neutrophils, which must be ≥ 1000/mm^3, and bilirubin, which must be ≤ the baseline grade).
b Hold and check weekly. ***With exception of neutrophils and bilirubin, resume treatment when toxicity is ≤ grade 1.*** If toxicity has not resolved to ≤ grade 1 after 3 weeks of delay, discontinue paclitaxel (see Section 11.2 for trastuzumab instructions for Group 2B).
c Only filgrastim on Days 2-6 may be used; pegfilgrastim is prohibited during paclitaxel.
d If grade 2 criteria for infection include topical antibiotics or other local treatment, use of G-CSF is at the investigator's discretion.
e Determination of "clinically significant" AEs is at the discretion of the investigator.

TABLE 26. Treatment management for paclitaxel-related neuropathy

Nervous System Disorders • Paresthesias • Peripheral sensory neuropathy	**1 – 7 Days Duration**	**Persistent for > 7 Days *or* Caused the Next Treatment to be Delayed**
Grade 1	Maintain paclitaxel dose	
Grade 2	Maintain paclitaxel dose[a]	Decrease paclitaxel one dose level[b]
Grade 3	**First episode:** Decrease paclitaxel one dose level[a] **Second episode:** Discontinue paclitaxel	Discontinue paclitaxel
Grade 4	Discontinue paclitaxel	

a Must be resolved to ≤ grade 1 on the next treatment day.
b Hold paclitaxel for ***persistent*** grade 2 neuropathy. When ≤ grade 1, resume treatment with dose modification for paclitaxel. If grade 2 toxicity persists after 3 weeks of delay, discontinue paclitaxel. (For patients in Group 2B, see Section 11.2 for instructions regarding trastuzumab.)

TABLE 27. Treatment management for **paclitaxel-related** musculoskeletal pain

Note: The treatment management instructions in Table 27 apply to patients with **musculoskeletal pain not controlled by analgesics**. Use of narcotics and NSAIDs is encouraged to maintain the paclitaxel dose if possible.

Musculoskeletal and Connective Tissue Disorders • Arthralgia • Myalgia	**1 – 7 Days Duration**	**Persistent for > 7 Days *or* Caused the Next Treatment to be Delayed**
Grade 1 *(despite analgesics)*	Maintain paclitaxel dose	
Grade 2 *(despite analgesics)*	Maintain paclitaxel dose	Maintain paclitaxel dose or Decrease paclitaxel one dose level*
Grade 3 *(despite analgesics)*	**First episode:** Decrease paclitaxel one dose level **Second episode:** Discontinue paclitaxel	**First episode:** Decrease paclitaxel one dose level* or Discontinue paclitaxel **Second episode**: Discontinue paclitaxel
* Hold paclitaxel for ***persistent*** grade 2 or 3 musculoskeletal pain. ***(Trastuzumab should be continued while paclitaxel is held.)*** When ≤ grade 1, resume treatment with dose modification. If grade 2 or grade 3 toxicity persists after 3 weeks of delay, discontinue paclitaxel. (For patients in Group 2B, see Section 11.2 for instructions regarding trastuzumab.)		

11.0 TRASTUZUMAB TREATMENT MANAGEMENT (GROUPS 2A AND 2B)

11.1 General instructions

- The CTCAE v4.0 must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- Treatment decisions should be based on the AE requiring the greatest modification.
- There are no reductions in the trastuzumab dose. If trastuzumab is held, the loading dose followed by the maintenance dose for the remaining doses may be administered, at the investigator's discretion, when resuming therapy.
- Trastuzumab must end 1 year (51–52 weeks) following the first trastuzumab dose regardless of any missed doses.
- *During weekly trastuzumab therapy for Group 2B patients*: The trastuzumab treatment schedule should be maintained. If necessary, the timing of a trastuzumab treatment may be adjusted to 3 days earlier or 3 days later than the scheduled date of treatment. However, no more than 2 trastuzumab doses may be given in a 2-week period.
- If trastuzumab must be discontinued before completion of the scheduled TC cycles (Group 2A) or WP cycles (Group 2B), the remaining TC or WP doses should be administered.
- If alternative (non-protocol) therapy is given at any time, study trastuzumab must be discontinued.
- In the event of tumor recurrence or diagnosis of a second invasive primary cancer, study trastuzumab must be discontinued. Further therapy is at the investigator's discretion.

11.2 Trastuzumab instructions when chemotherapy is held or discontinued

- When weekly paclitaxel is delayed for reasons not requiring a delay in trastuzumab, investigators are encouraged to continue trastuzumab. However, at the discretion of the investigator, trastuzumab may also be held. When docetaxel + cyclophosphamide is delayed, trastuzumab should also be held.
- With the exception of cardiac toxicity, pulmonary toxicity, or severe allergic or anaphylactic reaction (related to trastuzumab), trastuzumab therapy should continue even if chemotherapy has been discontinued before completion of all chemotherapy cycles.
- Refer to related instructions in Section 11.1.

11.3 Heart failure and left ventricular systolic dysfunction

11.3.1 *Symptomatic decrease in LVEF*

- *Grade 2, 3, or 4 heart failure*

  Discontinue trastuzumab.
- *Grade 3 or 4 left ventricular systolic dysfunction*

  Discontinue trastuzumab.

Note: The protocol-specified schedule for obtaining LVEF assessments should continue to be followed even after the discontinuation of study therapy or occurrence of a cardiac event.

11.3.2 *Asymptomatic decrease in LVEF*

- LVEF requirements for **initiation** of trastuzumab are addressed in Section 9.6 (Table 17).
- Patients in Group 2A and Group 2B will undergo scheduled 2-D echocardiograms (or MUGA scans) to assess the LVEF at 3, 6, 9, and 12 months following randomization (see Table 6).
- The results of the LVEF assessments during trastuzumab therapy will be used to determine if trastuzumab can be continued (see Table 28).
- Refer to Section 5.3 for LVEF reporting instructions.

TABLE 28. Trastuzumab management based on LVEF assessments **(Groups 2A and 2B)**

Table 28 provides instructions for patients who have an **asymptomatic decrease in LVEF** from baseline following any discretionary LVEF assessment during study therapy and at the scheduled assessment time points during therapy.

LVEF	**Asymptomatic decrease in LVEF percentage points from baseline**	
	Decrease of < 10 percentage points	**Decrease of ≥ 10 percentage points**
≥ 50%	Continue trastuzumab	Continue trastuzumab
45-49%	Continue trastuzumab and repeat echo/MUGA in 3 weeks	Hold trastuzumab and repeat echo/MUGA in 3 weeks
≤ 44%	Hold trastuzumab and repeat echo/MUGA in 3 weeks	Hold trastuzumab and repeat echo/MUGA in 3 weeks

Treatment rules based on "repeat" LVEF results:

- Trastuzumab must be discontinued when two consecutive "hold" categories occur.
- Trastuzumab must be discontinued when three intermittent "hold" categories occur.
- If LVEF is maintained at "continue trastuzumab and repeat LVEF" category or improves from "hold" to a "continue and repeat LVEF" category, additional LVEF assessments before the next scheduled LVEF will be at the investigator's discretion.

11.4 Other trastuzumab-specific instructions

Trastuzumab management for other adverse events is outlined on Table 29.

TABLE 29. Treatment management for **trastuzumab-related** adverse events **(Groups 2A and 2B)**

CTCAE v4.0 Adverse Event	CTCAE Grade	Action to be Taken
Cardiac Disorders		
Cardiac AEs listed in the Cardiac Disorders Section of the CTCAE v4.0. *(**Note:** For heart failure and left ventricular systolic dysfunction, refer to Section 11.3)*	1	Continue trastuzumab at the discretion of the investigator.
	2	Hold trastuzumab and conduct cardiac evaluation. Based on results of this evaluation, **refer to Appendix D for grade 2 AEs that require discontinuation of trastuzumab**. For other grade 2 cardiac AEs, trastuzumab should be held during evaluation of the AE and until ≤ grade 1; continue or discontinue at investigator's discretion.
	3, 4	Discontinue trastuzumab.
Gastrointestinal Disorders		
Diarrhea	2	Maintain dose without delay or hold trastuzumab until resolved to ≤ grade 1, then resume.
	3	Hold trastuzumab until resolved to ≤ grade 1, then resume.
	4	Discontinue trastuzumab.
General Disorders		
Infusion-related reaction	1, 2, 3, 4	See instructions for allergic reaction.
Immune System Disorders		
Allergic reaction	1	Slow the infusion and assess the patient; management is at the investigator's discretion.
	2	Stop infusion and administer support medications per investigator's discretion. When symptoms resolve to ≤ grade 1, infusion may be resumed later that day at a slower rate or on the next day at a slower rate with pre-meds. Pre-meds should be used for all subsequent treatments.
	3	Follow instructions for grade 2; trastuzumab may be discontinued at the investigator's discretion.
	4	Discontinue trastuzumab.
Anaphylaxis	3	Follow instructions for grade 3 allergic reactions or, at investigator's discretion, discontinue trastuzumab.
	4	Discontinue trastuzumab.
Respiratory, Thoracic, and Mediastinal Disorders		
ARDS	3, 4	Discontinue trastuzumab.
Cough	2, 3	Follow instructions in footnote **a**.
Dyspnea	1, 2, 3	Hold trastuzumab; rule out heart failure and non-infectious lung disease; follow instructions in footnote **a**.
	4	Discontinue trastuzumab.
Hypoxia	2, 3	Follow instructions in footnote **a**.
	4	Discontinue trastuzumab.
Pneumonitis	2	Follow instructions in footnote **a**.
	3, 4	Discontinue trastuzumab.
Pulmonary edema	2, 3	Follow instructions in footnote **a**.
	4	Discontinue trastuzumab.

(Table 29 is continued on the next page.)

TABLE 29. Treatment management for **trastuzumab-related** adverse events **(Groups 2A and 2B)** *(continued)*

CTCAE v4.0 Adverse Event	CTCAE Grade	Action to be Taken
Respiratory, Thoracic, and Mediastinal Disorders (continued)		
Pulmonary fibrosis	1	If fibrosis was present at baseline, trastuzumab may be continued at the investigator's discretion. If new or worsening fibrosis, discontinue trastuzumab.
	2, 3, 4	Discontinue trastuzumab.
Pulmonary hypertension	2, 3, 4	Discontinue trastuzumab.
Other		
Other clinically significant AEs[b]	2	Hold trastuzumab until ≤ grade 1 or discontinue trastuzumab.
	3, 4	Discontinue trastuzumab.

a Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 (if the AE requiring trastuzumab to be held was dyspnea) or when ≤ grade 1 (if the AE requiring trastuzumab to be held was ≥ grade 2).

b Determination of "clinically significant" is at the investigator's discretion and applies to those adverse events that *can be attributed to trastuzumab and are not related to chemotherapy*.

12.0 DRUG INFORMATION

12.1 Chemotherapy

Cyclophosphamide, docetaxel, doxorubicin, and paclitaxel will not be provided and must be obtained by the investigator from commercial sources. Please refer to current FDA-approved package insert provided with each drug for toxicity information and instructions for drug preparation, handling, and storage.

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13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Please refer to Coordinator Online in the Members' Area of the NSABP Web site for general information regarding adverse event (AE) reporting.

13.1 B-47 definitions for AE reporting

13.1.1 *Investigational agent*

The investigational agent administered in NSABP B-47 is trastuzumab, which is being made available under an IND sponsored by the National Cancer Institute (NCI). For patients who receive trastuzumab, expectedness of adverse events is based on the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER) for trastuzumab.

13.1.2 *Commercial agents*

The commercial agents in B-47 are cyclophosphamide, docetaxel, doxorubicin, and paclitaxel.

13.1.3 *Investigational combination therapy*

This study includes both investigational and commercial agents. When an ***investigational agent*** (trastuzumab) is administered concurrently or sequentially with a commercial agent (cyclophosphamide, docetaxel, doxorubicin, or paclitaxel) and an AE occurs that is expected for the commercial agent(s), but is not listed for trastuzumab, the AE should be considered expected for the combination. However, if based on clinical judgment, the investigator believes the adverse event is possibly, probably, or definitely related to the trastuzumab rather than the commercial agent(s), the AE should then be considered unexpected for the combination.

13.1.4 *Adverse event characteristics*

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP Web site (http://ctep.cancer.gov).

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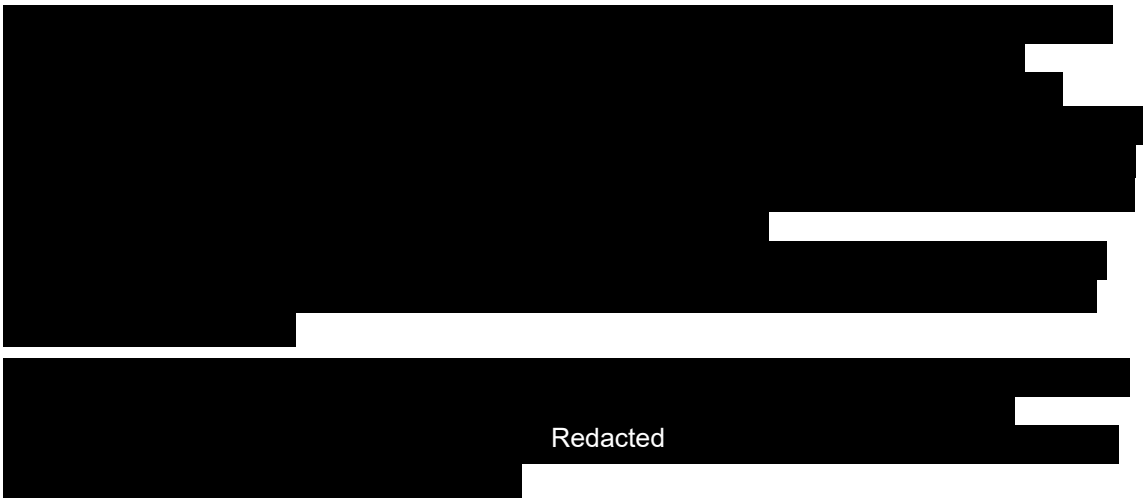

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13.3 Expedited reporting of adverse events

NRG Oncology follows procedures for centralized reporting of adverse events. Centralized reporting requires that adverse events be reported to the NRG Oncology SDMC. The NRG Oncology SDMC forwards reports to the appropriate regulatory agencies and the pharmaceutical company involved in the trial. Expedited reporting for B-47 utilizes the CTEP Adverse Event Reporting System (CTEP-AERS).

NRG Oncology is identified in CTEP-AERS as the Lead Group for NRG Oncology protocols that require CTEP-AERS reporting. **Expedited AE reporting for this study must be submitted to the NRG Oncology Lead Group** using CTEP-AERS, accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

13.3.1 *Expedited reporting methods*

- **CTEP-AERS 24 Hour Notification** requires that a CTEP-AERS 24-hour notification is electronically submitted to the NCI **within 24 hours** of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by either a CTEP-AERS 3 Calendar Day Report (see Table 31) or a CTEP-AERS 5 Calendar Day Report (see Table 32).
- **CTEP-AERS 3 Calendar Day Report** requires that a complete report is electronically submitted to the NRG Oncology Lead Group **within 3 calendar days** of submission of the CTEP-AERS 24-hour notification.
- **CTEP-AERS 5 Calendar Day Report** requires that a complete CTEP-AERS report is electronically submitted to the NRG Oncology Lead Group **within 5 calendar days** of the investigator learning of the adverse event.
- **Supporting documentation** is required for all CTEP-AERS reports. Include the protocol number, patient's ID number, and CTEP-AERS ticket number on each page, and **fax supporting documentation to the NRG Oncology SDMC (412-622-2113)**.

13.3.2 *Expedited reporting requirements – CTEP-AERS -24, CTEP-AERS, and other protocol requirements/exceptions*

- Expedited reporting requirements begin with the administration of the first chemotherapy dose. Expedited reporting requirements for all Groups 2A and 2B patients who receive trastuzumab are provided in Table 31. Expedited reporting requirements for Groups 1A and 1B patients are provided on Table 32.
- There are protocol-specific requirements and exceptions for expedited reporting. Refer to Table 31 and Table 32 for instructions.

13.3.3 *Other recipients of adverse event reports*

Adverse events determined to be reportable must also be reported by the investigator to the Institutional Review Board responsible for oversight of the patient according to the local IRB's policies and procedures.

13.3.4 *Expedited reporting requirements for patients receiving trastuzumab*

Expedited AE reporting requirements for Groups 2A and 2B patients receiving the investigational agent (trastuzumab) are listed in Table 31.

TABLE 31. CTEP-AERS expedited reporting requirements for adverse events that occur under a CTEP IND **within 30 days of the last dose of the investigational agent (trastuzumab)[1]**

Expected	Grade 1	Grade 2			Grade 3		Grade 4		Grade 5[2]	
	Unexpected and Expected	Unexpected with Hospital-ization	Unexpected without Hospital-ization	Expected	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required			Not Required		5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required		5 Calendar Days	Not Required	24-Hour; 3 Calendar Days	5 Calendar Days	24-Hour; 3 Calendar Days	5 Calendar Days

1 **Adverse events that occur <u>more than</u> 30 days after the last dose of investigational agent <u>and</u> have an attribution of possible, probable, or definite require reporting as follows:**

CTEP-AERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and grade 5 unexpected events

CTEP-AERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization
- Grade 5 expected events

2 **Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.**

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause should be provided.

- Expedited AE reporting timelines defined:
  "24 hours; 3 calendar days" – The AE must initially be reported via CTEP-AERS within <u>24 hours</u> of learning of the event followed by a complete CTEP-AERS report to the NRG Oncology Lead Group within <u>3 calendar days</u> of the initial 24-hour report.

  "5 calendar days" - A complete CTEP-AERS report on the AE must be submitted to the NRG Oncology Lead Group within <u>5 calendar days</u> of the investigator learning of the event.
- Any event that results in a persistent or significant disability/incapacity or a congenital anomaly/birth defect, or is an important medical event which based upon medical judgment may jeopardize the patient and require intervention to prevent a serious adverse event, must be reported via CTEP-AERS if the event occurs following investigational agent administration.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

(Table 31 is continued on the next page.)

TABLE 31. CTEP-AERS expedited reporting requirements for adverse events that occur under a CTEP IND **within 30 days of the last dose of the investigational agent (trastuzumab)[1]** *(continued)*

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur Under a CTEP-IND:

a) Reports submitted via CTEP-AERS 24-hour notification are available for review by both the NCI and NRG Oncology after submission. All other CTEP-AERS reports are first sent to the NRG Oncology Lead Group and then are forwarded to the NCI. The timelines in the table above have been set so that the information can be forwarded to the NCI in a timely manner per the NCI/CTEP's guidelines.

b) On all reports, use the NCI protocol number, CTEP-AERS ticket number, and the protocol-specific patient ID provided during the trial registration. **Fax supporting documentation to the NRG Oncology SDMC**.

c) Hospitalization: AE requires inpatient hospitalization for ≥ 24 hours, or prolongation of existing hospitalization.

d) Refer to Section 13.1.3 for instructions regarding assignment of attribution and expectedness for ***investigational combination therapy***.

e) CTEP-AERS reporting is required for grade 2 unexpected adverse events requiring hospitalization and grade 3 unexpected adverse events with or without hospitalization **only** if the adverse event is possibly, probably or definitely related to the **investigational agent**.

f) **Protocol-specific expedited reporting requirements**: For this study, the adverse events listed below require expedited reporting via CTEP-AERS to the NRG Oncology Lead Group **within 5 calendar days** (or sooner if required based on other Table 31 instructions) of learning of the event:

- Respiratory, Thoracic, and Mediastinal Disorders: ≥ grade 3 pneumonitis ***(NOTE: Requires expedited reporting via CTEP-AERS from the first dose of study therapy until 30 days after the last dose of the investigational agent [trastuzumab]).***
- Cardiac disorders regardless of attribution: ≥ grade 3 acute coronary syndrome; ≥ grade 2 heart failure; ≥ grade 3 left ventricular systolic dysfunction; ≥ grade 3 myocardial infarction ***(NOTE: These cardiac-related AEs require expedited reporting via CTEP-AERS from the first dose of study therapy until 2 years from randomization. Also, refer to Section 5.4 for additional instructions.)***
- Secondary malignancies as defined in Section 13.3.6 ***(NOTE: Secondary malignancies require expedited reporting via CTEP-AERS from the first dose of study therapy until the end of the patient's follow-up):***
  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

g) **Protocol-specific expedited reporting exceptions:** For this study, the adverse events listed below, including hospitalizations for these events, do **not** require expedited reporting via CTEP-AERS:

- Blood and lymphatic systems disorders: During chemotherapy, grade 3 and grade 4 febrile neutropenia. ***(Note: Beginning 30 days following the last dose of chemotherapy and when a patient is receiving trastuzumab alone, grade 4 febrile neutropenia requires expedited reporting and grade 3 febrile neutropenia possibly, probably, or definitely related to trastuzumab requires expedited reporting.***
- Investigations: During chemotherapy, grade 4 decreased neutrophil count, platelet count, and white blood cell count. ***(Note: Beginning 30 days following the last dose of chemotherapy and when a patient is receiving trastuzumab alone, these grade 4 events require expedited reporting.)***
- Neoplasms-malignant (i.e., a second primary malignancy) determined by the investigator to NOT be most probably related or definitely related to treatment for malignancy. (See footnote **f** and Section 13.6.)

13.3.5 *Expedited reporting requirements for patients receiving only chemotherapy*

Expedited AE reporting requirements for Groups 1A and 1B patients are listed in Table 32.

TABLE 32. CTEP-AERS expedited reporting requirements for adverse events that occur **within 30 days of the last dose of chemotherapy**

Attribution	**Grade 2**	**Grade 3**		**Grade 4[b]**		**Grade 5[a,b]**		**Protocol-Specific Requirements/ Exceptions**
	Un-expected	*Un-expected*	*Expected*	*Unexpected*	*Expected*	*Unexpected*	*Expected*	-See footnote **(c)** for other requirements -See footnote **(d)** for special ***requirements*** -See footnote **(e)** for special ***exceptions***
Unrelated or Unlikely				CTEP-AERS		CTEP-AERS		
Possible, Probable, Definite		CTEP-AERS if hospital-ized		CTEP-AERS 24 and CTEP-AERS		CTEP-AERS 24 and CTEP-AERS	CTEP-AERS	

CTEP-AERS-24: Indicates a CTEP-AERS 24-hour notification must be electronically submitted to the NCI and to the NRG Oncology Lead Group *within 24 hours* of learning of the event.

CTEP-AERS: Indicates a complete expedited report must be electronically submitted to the NRG Oncology Lead Group *within 5 calendar days* of learning of the event.

Hospitalization: AE requires inpatient hospitalization for ≥ 24 hours, or prolongation of existing hospitalization.

All Reports: On all reports, use the NCI protocol number, CTEP-AERS ticket number, and the protocol-specific patient ID provided during trial registration. ***Fax supporting documentation to the NRG Oncology SDMC.***

(Table 32 is continued on the next page.)

Table 32. CTEP-AERS expedited reporting requirements for adverse events that occur **within 30 days of the last dose of chemotherapy** (*continued)*

a) All deaths within 30 days of the last dose of study therapy require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided. **Although a CTEP-AERS expedited reporting requirements for adverse events that occur** within 30 days of the last dose of chemotherapy **24-hour notification is not required for death clearly related to progressive disease, a complete CTEP-AERS report is required as outlined in the table.**

b) Adverse events that occur greater than 30 days after the last dose of study therapy with attribution of possible, probable or definite to study therapy require reporting as follows:

- CTEP-AERS 24-hour notification followed by a complete CTEP-AERS report within 5 calendar days of learning of the event for:
  - grade 4 unexpected events
  - grade 5 unexpected events
- CTEP-AERS 5-calendar day report for:
  - grade 5 expected events

c) Any event that results in a persistent or significant disability/incapacity or a congenital anomaly/birth defect, or is an important medical event which based upon medical judgment may jeopardize the patient and require intervention to prevent a serious adverse event, must be reported via CTEP-AERS if the event occurs following chemotherapy administration.

d) **Protocol-specific expedited reporting requirements:** For this study, the adverse events listed below require expedited reporting via CTEP-AERS to the NRG Oncology Lead Group **within 5 calendar days** (or sooner if required based on other Table 32 instructions) of learning of the event:

- Respiratory, Thoracic, and Mediastinal Disorders: ≥ grade 3 pneumonitis ***(NOTE: Requires expedited reporting via CTEP-AERS from the first dose of study therapy until 30 days after the last dose of chemotherapy.)***
- Cardiac disorders regardless of attribution: ≥ grade 3 acute coronary syndrome; ≥ grade 2 heart failure; ≥ grade 3 left ventricular systolic dysfunction; ≥ grade 3 myocardial infarction ***(NOTE: These cardiac-related AEs require expedited reporting via CTEP-AERS from the first dose of study therapy until 2 years from randomization. Also, refer to Section 5.4 for additional instructions.)***
- Secondary malignancies as defined in Section 13.3.6 ***(NOTE: Secondary malignancies require expedited reporting via CTEP-AERS from the first dose of study therapy until the end of the patients follow-up):***
  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

e) **Protocol-specific expedited reporting exceptions:** For this study, the adverse events listed below which occur including hospitalization for these events, do **not** require expedited reporting via CTEP-AERS:

- Neoplasms-malignant (i.e., a second primary malignancy) determined by the investigator to NOT be most probably related or definitely related to treatment for malignancy. (See footnote **d** and Section 13.6.)

13.3.6 *Reporting a secondary malignancy*

A ***secondary malignancy*** is a cancer caused by a treatment for previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur on NCI-sponsored trials either during or following treatment must be reported via CTEP-AERS within 5 days of learning of the secondary malignancy (see either Table 31 or Table 32). Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Supporting documentation, including pathology and cytogenetics reports which confirm the secondary malignancy, must be faxed to the NRG Oncology SDMC expedited fax at 412-622-2113. Each page of supporting documentation must include the NCI protocol number, the CTEP-AERS ticket number, and the protocol-specific patient ID number provided during trial registration.

Note: All secondary malignancies should also be reported on the B-47 Form F (see Section 13.6).

13.3.7 ***Second malignancy***

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting online on the B-47 Form F (see Section 13.6).

13.3.8 ***Expedited reporting of pregnancy, fetal death, and death neonatal occurring during study therapy***

Any pregnancy, fetal death, or death neonatal occurring while the patient is receiving study therapy or within 6 months following the last dose of study therapy, if the patient is in Arm 1, or within 7 months following the last dose of study therapy, if the patient is in Arm 2, must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6) located at the following CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

Upon learning of a pregnancy, fetal death, or death neonatal that occurs during study or within 6 months following the last dose of study therapy, if the patient is in Arm 1, or within 7 months following the last dose of study therapy, if the patient is in Arm 2, the investigator is required to:

- Call the NRG Oncology Clinical Coordinating Department (see Information Resources)**.** ***Patients must immediately discontinue receiving study therapy.***
- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6):
  - Create and submit an CTEP-AERS report;
  - Complete the Pregnancy Information Form (located in the NSABP Members' Area in Protocol B-47 "Forms and Supporting Documents"); and
  - Fax the completed Pregnancy Information Form with all available supporting documentation to the NRG Oncology SDMC's expedited fax number at 412-622-2113.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Information Form used for the initial report.
- For questions concerning AE reporting, contact the AE Reporting Nurse (see Information Resources).

13.4 Routine reporting of adverse events

13.4.1 *Online reporting on the B-47 Treatment and Adverse Event Report form (Form TRTAE)*

- Direct online reporting of adverse events is done through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site.
- **Any grade 1 AE that required trastuzumab to be held or discontinued (see Table 29) and all ≥ grade 2 adverse events not reported via CTEP-AERS** that occurred during study therapy or during the 30 days following the last dose of study therapy must be reported on the B-47 Treatment and Adverse Event Report form (Form TRTAE).
- Supporting documentation for each adverse event must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, the online software will provide a transmittal form that must be printed. Fax this transmittal form with the supporting documentation to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.

13.4.2 *Schedule for submission of the B-47 Form TRTAE*

Form TRTAE is submitted online to the NRG Oncology SDMC, **even if no AEs were experienced by the patient**, according to the following schedule:

- All patients receiving chemotherapy with or without trastuzumab
  - *During TC and AC:* Submit Form TRTAE at the end of each cycle of chemotherapy.
  - *During paclitaxel:* Submit Form TRTAE after every 3 doses.
  - *After the final dose of chemotherapy for patients not receiving trastuzumab:*

    Submit Form TRTAE 30 days after the final dose of chemotherapy.
- All patients receiving trastuzumab
  - *During trastuzumab (given without chemotherapy):* Submit Form TRTAE every 9 weeks, if no treatment delay.
  - *After the final dose of trastuzumab:* Submit Form TRTAE 30 days after the final dose of trastuzumab. (The final Form TRTAE will include the time period from the most recent Form TRTAE through 30 days after the last trastuzumab dose.)

13.5 Reporting selected late cardiac adverse events on the B-47 Follow-up Form (Form F) and Form CR

Beginning at year 3 and continuing through year 10, the selected late cardiac adverse events listed below will be reported online on B-47 Form F and Form CR for all patients. **(Also, refer to Section 5.6 regarding required additional follow-up when late heart failure or left ventricular systolic dysfunction are reported.)**

- ≥ grade 3 acute coronary syndrome
- ≥ grade 2 heart failure
- ≥ grade 3 left ventricular systolic dysfunction
- ≥ grade 3 myocardial infarction

Note: Supporting documentation must be submitted for each adverse event listed above and must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, the online software will provide a transmittal form that must be printed. Fax this transmittal form with the supporting documentation to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.

13.6 Reporting breast cancer recurrence, secondary malignancies, and second primary cancer

Report breast cancer recurrence, secondary malignancies (including leukemia secondary to oncology chemotherapy, myelodysplastic syndrome, and treatment-related secondary malignancy previously reported through CTEP-AERS), and second primary cancer (a malignancy which is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) online on the B-47 Form F. Fax supporting documentation, unless previously faxed to the NRG Oncology SDMC with an CTEP-AERS report, that confirms the breast cancer recurrence or second primary cancer diagnosis with the transmittal form (provided by the online software and printed) to 412-622-2111.

14.0 DOCUMENTATION OF BREAST CANCER RECURRENCE AND SECOND MALIGNANCIES

14.1 General instructions

- Documentation of a breast cancer recurrence requires meeting at least one of the criteria defined below. Suspicious findings do not provide adequate documentation of a breast cancer recurrence, and should not be an indication to alter protocol therapy.
- Tumor marker evaluations alone do not document breast cancer recurrence.
- Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.

14.2 Local recurrence

Note: If the first local recurrence is non-invasive breast cancer, the first invasive breast cancer must also be reported.

Recurrent local tumor is defined as evidence of invasive breast cancer or DCIS in the ipsilateral breast or invasive breast cancer in the skin of the ipsilateral breast. Patients who develop clinical evidence of local recurrence in the ipsilateral breast must have a biopsy confirmation of recurrence. However, if a patient also meets criteria for regional or distant metastatic disease, results of clinical exams alone will be sufficient to document local recurrences.

14.2.1 *Ipsilateral breast tumor recurrence (IBTR)*

An IBTR event is defined as recurrent invasive or non-invasive breast cancer in the ipsilateral breast parenchyma or invasive breast cancer in the skin of the breast occurring after lumpectomy.

Acceptable documentation includes core, incisional or excisional biopsy. Cytology alone will not be adequate to establish IBTR.

14.2.2 *Other local recurrence*

Defined as recurrence in the skin of the chest wall (exclusive of the breast) or chest wall.

Acceptable documentation includes core, incisional or excisional biopsy, as well as cytology.

14.3 Regional recurrence

Defined as the development of tumor in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, following surgery. Recurrence must be confirmed by biopsy or cytology. However if a patient meets criteria for distant metastatic disease, results of clinical exams alone will be sufficient to document regional recurrences.

14.4 Distant recurrence

Defined as evidence of tumor in all areas, with the exception of those described in Sections 14.2 and 14.3. **The first distant recurrence and the first central nervous system recurrence will be reported.** Further treatment for distant metastasis, with or without evidence of local-regional recurrence, will be at the discretion of the investigator.

14.4.1 *Skin, subcutaneous tissue, and lymph nodes (other than local or regional)*

Acceptable documentation includes positive cytology, aspirate or biopsy, or radiologic evidence of metastatic disease.

14.4.2 *Bone marrow*

Acceptable documentation includes positive cytology, aspirate, biopsy, or MRI scan.

14.4.3 *Lung*

Acceptable documentation includes: (i) positive cytology, aspirate, or biopsy, or (ii) radiologic evidence of multiple pulmonary nodules that are judged to be consistent with pulmonary metastases.

Note: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT scan, or MRI scan, further investigations, such as biopsy, needle aspiration, PET-CT scan, or PET scan should be performed. Proof of neoplastic pleural effusion must be established by cytology or pleural biopsy.

14.4.4 *Skeletal*

Acceptable documentation includes: (i) x-ray, CT, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, (ii) biopsy proof of bone metastases, or (iii) bone scan, PET-CT scan, or PET scan clearly positive for bone metastases.

Note: If the diagnosis is equivocal by bone scan or radiologic evaluation, a biopsy is strongly recommended. A bone scan with uptake limited to joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

14.4.5 *Liver*

Acceptable documentation includes: (i) abdominal CT scan, liver scan, ultrasound, MRI, PET-CT scan, or PET scan consistent with liver metastases, or (ii) liver biopsy confirmation of the metastatic disease.

Note: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

14.4.6 *Central nervous system*

Acceptable documentation includes: (i) positive CT scan, PET-CT scan, PET scan, or MRI scan, usually in a patient with neurological symptoms, or (ii) biopsy or cytology (for a diagnosis of leptomeningeal involvement).

14.5 Contralateral breast cancer

Contralateral breast cancer is defined as evidence of invasive breast cancer or DCIS in the contralateral breast or chest wall. The diagnosis of a contralateral breast cancer must be confirmed by core, incisional, or excisional biopsy. Cytology alone will not be adequate to document a contralateral breast cancer.

14.6 Second primary cancer

Second primary cancer is defined as any ***invasive*** non-breast cancer other than squamous or basal cell carcinoma of the skin. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

14.7 Documentation requested following death

- Autopsy reports should be secured whenever possible and should be submitted to the NRG Oncology SDMC.
- A copy of the death certificate should be forwarded to the NRG Oncology SDMC if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Please submit the last clinic/office note made before the death or the investigator's note summarizing events resulting in death.

15.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

Note: Accrual closed on February 10, 2015, following achievement of the sample size goal.

15.1 CTEP investigator registration procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

15.2 CTEP associate registration procedures / CTEP-IAM account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

15.3 CTSU registration procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

15.3.1 *IRB approval*

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

15.3.2 *Downloading site registration documents*

Site registration forms may be downloaded from the NSABP B-47 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the NCTN Groupname link to expand, then select trial protocol NSABP B-47
- Click on the Site Registration Documents link

15.3.3 *Requirements for protocol number site registration*

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

15.3.4 *Submitting regulatory documents*

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (Members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

15.3.5 *Checking your site's registration status*

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

15.4 Patient consent form

Before the patient is enrolled, the consent form, including any addenda, must be signed and dated by the patient and the person who explains the study to that patient.

15.5 Patient enrollment

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

15.6 Required submission of tumor samples

As part of the B-47 consent form, all patients have agreed to allow the submission of tumor blocks (see Section 7.1).

15.7 Regulatory requirement for Canadian institutions

Any Canadian institution that will utilize PET scans in the conduct of this study *must* indicate the intent to do so to the NRG Oncology Department of Regulatory Affairs *prior to initiating patient enrollment at the institution (and any satellites)*. Use of PET scans as part of this study may require submission by NRG Oncology of specific documentation to Health Canada before activation of the trial at the institution.

15.8 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. (Site staff should use the registration forms provided on the NRG Oncology or CTSU Web site as a tool to verify eligibility.)
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

  Note: The OPEN system will provide the site with a printable confirmation of registration, including the Patient ID number for the study, and treatment information. Please print this confirmation for your records. Additionally, a transmittal form to be used when faxing the signed consent form to the NRG Oncology SDMC will be provided. If it is necessary to reprint the randomization confirmation or the transmittal form, they can be reprinted through Coordinator Online via the ***View a Patient Entry Report*** under Patient Entry.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU Web site at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

15.9 Patient study number

After randomization, the institution will receive the Patient ID number for the study.

15.10 Patient-initiated discontinuation of study therapy

Even after a patient agrees to take part in this study, she may stop study drug or withdraw from the study at any time. If study therapy is stopped but she still allows the study doctor to submit information, study data and other materials must be submitted according to the study schedule, including any Menstrual History study and Host Factors study assessments and blood samples, as well as any correlative science tumor and blood samples.

15.11 Withdrawal from the study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to NRG Oncology SDMC), the investigator must provide the NRG Oncology SDMC with written documentation of the patient's decision to fully withdraw from the study.

15.12 Investigator-initiated discontinuation of study therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study drug if one of the following occurs:

- the patient develops a serious side effect that she cannot tolerate or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study drug or other treatments for breast cancer becomes available.

If study therapy is stopped but she still allows the study doctor to follow her care, she should continue to be followed according to the study schedule.

16.0 REQUIRED DATA COLLECTION

16.1 Data collection

B-47 data collection will include the following elements:

- Patient characteristics
- Menstrual history as described in Section 8.2
- Concomitant medications
- Tobacco and alcohol use
- Comorbid conditions
- Weight and height
- Characteristics of the breast cancer
- AJCC TNM stage
- Study treatment administered
- Other treatment including RT and endocrine therapy
- LVEF assessments
- Cardiac events as described in Sections 5.4, 5.5, and 5.6
- Adverse events as described in Section 13.0
- Breast cancer events (local, regional, and distant)
- Second primary cancer events
- Survival

16.2 Instructions for completion and submission of B-47 forms and materials

- Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and other documents directly to the NRG Oncology SDMC. Submission of study data directly to NRG Oncology is done through the Online Data Entry function located in the Study Management Area of Coordinator Online in the Members' Area of the NSABP Web site. Contact the Support Desk at support@nrgoncology.org for an account. When submission of supporting documentation to the NRG Oncology SDMC is required, fax to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation.
- The NRG Oncology SDMC will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the NRG Oncology SDMC and do not copy the CTSU Data Operations. If the query is sent with fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.
- Data form worksheets and specimen transmittal forms, as well as instructions for completion and submission of data and materials, are available in the Members' Area of the NSABP Web site, http://www.nsabp.pitt.edu. (CTSU investigators should refer to the NSABP B-47 Web page located on the CTSU Member site.) Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

16.3 Data monitoring for CTEP

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. CTEP has assigned abbreviated CDUS reporting: no AE reporting (routine or expedited) is required via any of the CDUS mechanism. Cumulative CDUS data will be submitted quarterly by the NRG Oncology SDMC by electronic means. Reports are due January 31, April 30, July 31, and October 31.

17.0 STATISTICAL CONSIDERATIONS

17.1 Primary endpoint

The primary endpoint for efficacy analysis is invasive disease-free survival (IDFS) (see Section 3.1).

17.2 Secondary endpoints

Secondary efficacy endpoints include disease-free survival (DFS-DCIS), breast cancer-free survival (BCFS), recurrence-free interval (RFI), distant recurrence-free interval (DRFI), and overall survival (OS). Secondary safety endpoints include the frequency and severity of adverse events graded according to the CTCAE v4.0. (See Section 17.9 for additional endpoints related to the Menstrual History and Host Factors sub-studies.)

17.3 Stratification and randomization

Assignment of treatments to patients will be balanced with respect to IHC score (1+, 2+), pathologic nodal status (0-3, 4-9, 10+ positive nodes), hormone receptor status (ER-positive and/or PgR-positive, ER- and PgR-negative), and intended chemotherapy regimen (TC, AC→WP) as specified prior to randomization, using a biased-coin minimization algorithm.[101]

17.4 Patient cohorts

The primary objective of this trial is to show that the addition of trastuzumab to chemotherapy (either TC [Groups 1A and 2A] or AC→WP [Groups 1B and 2B]) improves IDFS. Patients will be entered in one of these two chemotherapy cohorts based on the investigator's preference, which must be indicated prior to randomization.

17.5 Sample size calculation

17.5.1 *Estimates of annual hazard rates*

We have estimated yearly hazard rates for IDFS events in breast cancer patients treated with TC reported in Jones et al.[61] We approximated the total person years by first multiplying the number of patients in the TC arm by the median follow-up in months and then by dividing it by 12 to make it an annual rate, i.e., (506 x 66)/12=2783.

Based on this estimate of the total person years, the annual hazard rate was estimated as 0.028 (=79/2783). Here the 79 events include recurrence or second primary cancer, and death without recurrence from Table 2 in Jones et al.[61]

17.5.2 *Accrual rate and total sample size*

This protocol will be attractive to patients similar to those who participated in the NSABP B-36 and B-38 trials. Based on our experience in those trials, it is realistic to assume an eventual steady-state accrual of 100 patients per month. To account for delays in getting the trial approved by local IRBs and initiated at each potential site of accrual, we assume linear ramp-up from 10 to 100 patients per month during the first year of accrual. A steady monthly accrual of 100 patients was assumed thereafter.

The total accrual to the trial will be 3,260 patients. This sample size will provide statistical power of 0.9 to detect a 33% reduction in the hazard rate among the chemotherapy plus trastuzumab group compared to the chemotherapy alone group using a one-sided alpha level of 0.025. The projected time to reach this accrual goal is 3 years and 2 months.

17.6 Statistical analysis

17.6.1 *Primary efficacy analysis: Compare the chemotherapy plus trastuzumab group to the control group (chemotherapy alone) with respect to IDFS*

Timelines: We will perform the definitive analysis comparing chemotherapy plus trastuzumab to Control (chemotherapy alone), using IDFS as the primary endpoint, when 262 events have occurred in total on the Control + chemotherapy/trastuzumab arms. The comparison will be performed using a log rank test.

- The estimated time required to accrue 3,260 patients is 3 years, 2 months.
- The estimated time to reach the required number of events is 5 years and 6 months from the start of accrual.
- Allowing an additional 6 months for reporting and data lock, the total time from start of accrual to analysis will be roughly 6 years.

17.6.2 *Interim efficacy analyses*

There will be three interim analyses. The first interim analysis will take place at the first regularly scheduled meeting of the NRG Oncology Data Monitoring Committee (DMC) when 66 events have occurred in total on the Control (chemotherapy alone) + chemotherapy/trastuzumab arms. Subsequent interim analyses will take place according to the schedule outlined on Table 33.

TABLE 33. Interim monitoring schedule

Interim and final analysis (k)	Approximate number of events in each comparison	Lower significance level (for futility)	Upper significance level
1	66	0.01	0.0001
2	131	0.05	0.00025
3	197	0.3	0.00025
Final analysis	262	N/A	0.0246

At each interim analysis, the experimental arm (chemotherapy plus trastuzumab) will be compared to the control arm (chemotherapy alone) using IDFS as the primary endpoint. At each interim analysis, crossing the upper boundary will indicate that the experimental arm is significantly better than the control arm at a pre-specified nominal level given in Table 33. If that happens, the DMC will consider declaring the experimental treatment to be superior to the control and terminating the study. We expect that one-sided type I error probability for the definitive analysis will be approximately 0.0246.

At each interim analysis, the experimental arm will also be tested against the control arm to see whether the study should be stopped due to futility (see Table 33). For example, at the first interim analysis, consideration will be given to stopping the study if the experimental arm is significantly worse than the control arm with one-sided significance level of 0.01.

Under our data management system, summary files are locked every 3 months for approval, so in practice the numbers of events at each interim analysis may differ slightly from the numbers given in Table 33. If significant deviations are necessary, the parameters will be adjusted by alpha-spending[102] to insure that the type 1 error control criteria cited above are maintained.

17.7 Monitoring of adverse events

The occurrence of adverse events, including toxicities and deaths, will be monitored. Summaries of all adverse events will be prepared and discussed at regularly scheduled meetings of the NRG Oncology Medical Affairs Division.

In addition, throughout the periods in which the protocol is open to accrual or patients are receiving therapy, semi-annual progress reports will be made to the NRG Oncology DMC. These reports will include an assessment of toxicities, including cardiac events as described in Sections 5.4, 5.5, and 5.6 and deaths during study therapy; a comparison of actual and projected accrual; and an assessment of data quality, including data delinquency and rates of eligibility. After accrual is closed, reports of adverse events, together with the results of planned interim analyses of the primary endpoints will be presented in semi-annual progress reports to the DMC.

17.8 Sample size considerations and analysis plan for correlative studies dealing with HER2 mRNA and Fcγ receptor polymorphism

A sample size of 2,500 will be sufficient to evaluate an interaction between HER2 mRNA and treatment. This is based on the conservative case of dichotomized expression level thereby dealing with a 2-by-2 table. We assume that the probability of falsely rejecting the null hypothesis of no interaction is 10%. By using the results proposed in Peterson and George[103] with the sample size of 2,500, the probability of detecting the interaction hazard ratio of 0.5 is expected to be 81%. The same cohort of patients will be used to validate Fcγ receptor polymorphism as a predictor.

The interaction between treatment effect and HER2 mRNA level will be evaluated in the proportional hazards model[104], which would include an indicator for treatment group and the HER2 mRNA level as a continuous variable, and the corresponding interaction term. The log-hazard ratio plot for the interaction term with 95% confidence intervals will be used to determine the cut-off of the HER2 mRNA level that would determine a subset of the patients who would benefit from the adjuvant trastuzumab therapy. The polymorphism of the Fcγ 158 receptor gene will be dichotomized as V/V (valine) vs. other genotypes and the polymorphism of the Fcγ 131 receptor gene will be dichotomized as H/H (histidine) vs. other genotypes to evaluate an interaction between treatment group and Fcγ polymorphism. The Kaplan-Meier method[105] will be used to estimate the distribution of the primary endpoints stratified by the dichotomized subgroups, and the log-rank test[106] will be used to statistically compare the time-to-event distributions.

The potential association between response with anthracycline and HER2 level could impact on estimated trastuzumab benefit differently in the two chemotherapy groups. To investigate this, an interaction between HER2 level and treatment with/without anthracycline will be evaluated. If there is a significant interaction at the 2-sided level of 0.05, it will be included as an adjusting factor for the main analysis.

17.9 Statistical considerations for Menstrual History and Host Factors sub-studies

17.9.1 *Menstrual History sub-study analyses*

The primary endpoints for the MH sub-study are amenorrhea (cessation of menses for ≥ 6 months), circulating ovarian hormone suppression (the following set of conditions: low levels of estradiol and elevated levels of FSH), and duration of amenorrhea. The time to amenorrhea and time to hormone suppression will be censored if a patient undergoes a hysterectomy with or without oophorectomy, and will also be censored at the time of a new cancer event, death, or last follow-up in the absence of any of the specified events. Statistical tests will be two-sided. The two primary analyses will be tested at significance level 0.05/2. All secondary and exploratory analyses will be performed at significance level 0.05, without adjustment for multiple comparisons, and reported as secondary or exploratory. In the Cox regressions described below, we will test the proportional hazards assumption by creating an artificial time-dependent covariate and testing its interaction with other covariates, as described in Klein and Moeschberger, and will explore more appropriate models if the assumption is not satisfied.[107]

Hypotheses in Section 8.2.7 will be tested as follows. Primary hypothesis (a) will be tested using a kappa test for agreement between two raters, to determine whether patients with amenorrhea are more likely to have hormone suppression, including data from 6 and 12 months to determine whether amenorrhea and hormone suppression have occurred. This test will be performed without regard to treatment assignment or other predictors of amenorrhea because the objective is to determine whether these two approaches to detecting amenorrhea coincide, although in exploratory analyses we may examine whether the approaches have greater agreement within subgroups of patients. For primary hypothesis (b), the fraction of patients with amenorrhea will be compared between treatment groups according to the random assignment using a Binomial test of two proportions. An exploratory examination will consider only patients with positive ER status. For this analysis and for secondary hypothesis (b), we will use the full time course of amenorrhea. The denominator for the proportions will be the number of patients who had at least one MH follow-up. However, any bias in the compliance with MH assessments between treatment groups will also bias these analyses because more assessments provide a greater opportunity to observe amenorrhea. We will address this as described below under "Missing Data."

Secondary hypothesis (a) will be tested using Cox proportional hazards regression of the time from establishment of amenorrhea (time at which ≥ 6 months of amenorrhea are first observed; that is, 6 months after the last bleeding) to the resumption of menses, with explanatory factors age (< 40, 40–49, ≥ 50), TC regimen, use of tamoxifen, or ovarian suppression therapy (e.g., GnRH analog therapy), and baseline hormonal profile (i.e., low estradiol and elevated FSH). We will also include ER and PR status and two-way interactions of those with TC regimen. This analysis includes only those patients who have amenorrhea.

For secondary hypothesis (b), we will use Cox proportional hazards regression of the time from randomization to onset of amenorrhea (date of last period before > 6 months of amenorrhea as reported by the patient to the coordinator), with explanatory factors TC regimen (the factor of interest), age (< 40, 40–49, ≥ 50), use of tamoxifen, or ovarian suppression therapy (e.g., GnRH analog therapy), and baseline hormonal profile (i.e., low estradiol and elevated FSH). We will also include ER and PR status and two-way

interactions of those with the TC regimen. The analysis of time to onset of hormone suppression will be handled differently because hormone suppression will only be detected as of the time of a blood draw. We will use ordinal logistic regression (classifying onset time as 6 months, 12 months, etc.), including the same list of explanatory variables.

To test secondary hypothesis (c), we will conduct model building and internal validation using four-fold cross-validation.[108] We first randomly divide the sub-study patients into four subsets of equal size, stratified by age (< 40, 40–49, ≥ 50) and TC regimen. Combining three of the subsets into a training set, we will perform weighted logistic regression, classifying women as having developed early, permanent amenorrhea (no return of menses at 36 months, with amenorrhea duration ≥ 30 months) versus all others. A fraction of women will not be evaluable for permanent amenorrhea due to cancer recurrence, death, or missing data for other reasons. Women whose disease-free survival is shorter than 36 months will not be considered in this analysis, and the results will be viewed as conditional on being alive and disease-free at 36 months. To account for data that are missing for other reasons, we will use a propensity score approach, first performing a logistic regression for evaluable status using the same factors listed below for this hypothesis. The propensity scores will then be used to define weights for the logistic regression of permanent amenorrhea. Explanatory variables will be demographic and behavioral factors (age, weight, ethnicity, current tobacco use, prior hormone use), medical (treatment assignment-cytoxan duration), menstrual history (bleeding patterns in year prior to diagnosis), and baseline ovarian hormones. Variables that are not significant at the 0.10 level in this multivariable analysis will be removed from the final model. (A liberal significance level is used because prediction is the goal rather than model parsimony or tests of the significance of individual variables.) To evaluate whether the predictive model is useful, we will then apply the estimated factor coefficients to the data in the remaining quarter subset (the test set) and compute the sensitivity, specificity, and the negative and positive predictive values. This process of model building and testing will be repeated three additional times by leaving out one-quarter each time. The means and standard errors of sensitivity, specificity, and the negative and positive predictive values will be reported. A final model will then be constructed using the same approach, including all evaluable patients.

To test secondary hypothesis (d), we will conduct a landmark Cox regression analysis of the time from the 6-month blood draw to the first invasive cancer event or death. The time will be censored at the last follow-up in the absence of an invasive cancer event or death. The explanatory factors will be circulating hormone suppression as of the 6-month sample, chemotherapy and trastuzumab treatment, stratification factors used in the randomization, and interaction terms between hormone receptor status and TC regimen. The same 6-month landmark analysis will be used to test the prognostic significance of amenorrhea at 6 months. However, for this analysis we will consider women amenorrheic if their most recent bleeding occurred at least 3 months prior. (In this way, we will include amenorrhea that began in response to chemotherapy.)

To test secondary hypothesis (e), we will assess associations between genetic variants and CRA (defined as no periods between the end of chemotherapy and the last available menstrual follow-up). We will pool our genome-wide association data with data from other large clinical trials to obtain a sample size of 2800. Analyses will be adjusted for study, time from last dose of chemotherapy to last follow-up, BMI, age, chemotherapy regimen (grouping those with similar doses of alkylating agents and anthracyclines), and

endocrine therapy (including time on and time since last ovarian function suppression medication administration) because other studies have shown that these variables may all impact risk of CRA. An individual's genotype for each SNP will be coded to represent the number of copies of the minor allele that she carries. We will assign individuals to major racial groups by comparing genome-wide genotypes to 1000 Genome reference data using the software STRUCTURE and REAP. These methods provide estimates of the probability a patient belongs to a major racial group, and we assign each patient to a genetically defined race group based on the maximum probability. We will focus the primary analysis on genetically defined White and non-Hispanic patients to optimize our power. To further adjust for population stratification within a genetically defined race group, we will estimate principal components based on all SNPs, using EIGENSTRAT software.[109] Then, stratifying on race, we will evaluate whether additional covariates associated with the CRA should be used as adjusting factors. Covariate selection will be performed within each stratum based on p-values for covariates < 0.1 (a somewhat liberal threshold).

Once each stratum of race has clearly defined principal components and adjusting covariates, we will perform a GWAS analysis within White non-Hispanics. Tests of association between SNPs and CRA will be performed using R or PLINK statistical software, based on logistic regression. We will explore other tools appropriate for data-rich situations including approaches that assess for an over-abundance of small p-values within specific pathways identified in the literature, and using classification and regression trees to identify other combinations of SNPs associated with CRA. To reduce false positives, we will adhere to the common practice of using a p-value threshold of 5x10-8.

To test secondary hypothesis (f), we will evaluate AMH as a biomarker for CRA. We will pool these data with data from other clinical trials (total N=2900), and treat AMH as a continuous covariate in a logistic model for CRA, adjusting for other covariates (e.g., age, BMI, chemotherapy regimen received, endocrine therapy, and months of ovarian function suppression). We will assess whether or not AMH should be modeled with a linear effect versus a more flexible model using natural cubic splines. Two-sided p-values < 0.05 will be considered significant. We also plan an exploratory analysis of the association of AMH with time to menstruation using a Cox proportional hazards model with time-dependent covariates, and we will model the interaction between AMH and each of the SNPs that were found to be associated with CRA.

17.9.2 *Host Factors sub-study analyses*

The primary endpoint for the Host Factors sub-study is invasive disease-free survival (defined in Section 3.1). Time is measured from randomization except in landmark analyses described below. Primary and secondary hypotheses will be tested using Cox proportional hazards regression. General statistical considerations will follow those in Section 17.9. Hypotheses in Section 8.3.7 will be tested as follows.

For primary hypothesis (a), the explanatory factors will be baseline BMI, tobacco and alcohol use, comorbid conditions, trastuzumab group, chemotherapy regimen, and stratification factors. Primary hypothesis (b) will be tested with a landmark analysis in which event time will be measured from 1 year and the analysis will include only those patients who are alive and free of invasive cancer as of 1 year. The explanatory variables will be the same as for hypothesis (a) except with the addition of the slope of BMI from

baseline to 1 year. The effect of overweight in hypothesis (a) and effect of weight change in hypothesis (b) will be tested at significance level 0.05/2.

For secondary hypothesis (a), explanatory variables will include baseline use of metformin, aspirin, NSAIDs, beta blockers, ACE inhibitors, and ARBs, as well as baseline BMI, tobacco use, alcohol, and comorbid conditions. Exploratory analyses will include interactions among metformin, aspirin, NSAIDs, ACE inhibitors, and ARBs, and beta blockers, and will also consider the use of these agents over time as a time-varying factor. Hypothesis (b) will be tested with two Cox regression analyses: one using only baseline CRP elevation (and other factors listed above), and the second using elevation of CRP at baseline and/or 12 months, using a landmark approach at 12 months. The landmark analysis will include only patients who are alive and free of invasive cancer at 12 months and who are evaluable for CRP at both baseline and 12 months. In addition, we will test whether the effect of BMI is mediated by its impact on CRP. To do this, we will add CRP elevation to the model with BMI. If the effect of BMI is diminished, that will support mediation. The development and validation of the predictive model for hypothesis (c) will follow the four-fold cross-validation approach described above for amenorrhea. The modeling will be performed with Cox regression as in other analyses for this sub-study. For hypothesis (d), all above primary and secondary analyses will be repeated with a secondary endpoint, recurrence-free interval (defined in Section 3.2.3), using competing risk models if needed.

17.9.3 *Evaluable data for Menstrual History and Host Factors analyses*

All analyses will be performed including all enrolled patients who have data available for the given analysis. Analyses involving blood markers will be conducted only with patients who consented to providing blood samples for this research.

17.9.4 *Missing MH or Host Factors data*

Completion of all scheduled questionnaires is part of the routine delinquency assessment for centers collaborating in B-47. Adherence to the questionnaire assessment schedule will be encouraged by means of proactive reminders to the participating institutions and other measures that have previously been found effective.[110] The NRG Oncology SDMC staff will continue to monitor proportions of missing information occurring in each treatment arm at different assessment points. If a decline in follow-up assessments is observed in specific centers or specific trial arms, interventions will be developed to address problems in the data collection process. If all efforts to collect a scheduled questionnaire fail, the center will be required to submit a missing data form. This form will capture the reason for the missing data and will enumerate the attempts made by clinic staff to collect the questionnaire.

Despite these precautions, some missing data is expected. Because the analysis for secondary hypothesis (c) for the MH sub-study requires data at 36 months, and is therefore most likely to have missing data, that analysis includes propensity score weighting as described above. In general, information from patients with missing data will be reviewed to detect sources of bias. Patients with missing data will be reviewed for imbalances in factors such as trial arm, treatment adherence, collaborating center, and reasons for non-adherence. If no missing data mechanism can be detected, the data will be analyzed assuming the missing data are at random. If a missing data mechanism appears to be present, we will develop an appropriate analytic strategy to control for the

potential bias and, if possible, to impute the missing values. The appropriateness of alternative strategies will depend upon both the pattern (e.g., item non-response versus intermittent missing forms versus complete dropouts) and the severity of the missing data problem.[111-113] For example, an appropriate strategy could involve the stratification of the patients in the study in terms of the completeness of their data for key time periods (e.g., 6 months or 1 year) and the comparison of results from separate analyses for each group or it could involve the implementation of more sophisticated imputation procedures designed to model a missing data mechanism.[114,115] We will also present sensitivity analyses based on varying assumptions about the missing-data mechanism.

17.9.5 *Statistical power for MH and Host Factors sub-studies*

We expect to enroll 1500 patients who will be eligible for the MH sub-study. In NSABP B-30, sufficient follow-up data were available to analyze 87% of enrolled MH sub-study patients. An evaluable sample size of 1500x87%=1305 will provide 80% power to detect a kappa coefficient of 0.09 against a null value of 0, assuming that the percentage of women with amenorrhea by 12 months is approximately 79% (as in the AC→T arm of B-30). (The power calculation applies for percentages in the range of 20-80%, as seen in various treatment groups of B-30.) For primary hypothesis (b), n=1305 will provide 80% power to detect a difference in the proportion amenorrheic of 0.79 versus 0.86 or 0.79 versus 0.71 (tested at the 0.025 significance level). For secondary hypothesis (a), assuming 79% of women become amenorrheic at some point during the study, the sample size will be 79% x 1305=1031. This will provide 80% power to detect the effect of a variable, assuming that variable has standard deviation 1.0, the hazard ratio is 1.33, other variables in the regression model have a joint R^2 of 0.1, and 10% of patients resume menses during the study (again, using observations from B-30).

In the Host Factors sub-study, the sample size for the questionnaire data is 3260 (all B-47 patients). With 262 events at the time data are locked for the primary analysis for the parent B-47 study (see Section 17.6.1), this will provide 80% power to detect the effect of BMI, assuming the hazard ratio is 1.22 corresponding to a one standard deviation change in BMI, and assuming that when BMI is regressed on other variables in the model, the R^2 is 0.1. For the second primary analysis, the following considerations apply. We expect 3168 patients to be alive and free of invasive disease at one year, and therefore eligible for the landmark analysis (using the expected annual event rate of 0.028 per Section 17.5.1). We assume that a random sample of 90%, or 2851, will also have adequate questionnaire data at 1 year (a conservative assumption relative to rates of questionnaire compliance in past NSABP studies; note that the 87% figure cited above also included attrition due to disease events). Among those patients, we would expect 154 (90%) of the remaining 171 IDFS events expected to occur after 1 year and before the data lock. This will provide 80% power to detect the effect of the slope of BMI, assuming the hazard ratio is 1.30, and other assumptions are as above. Power calculations were performed in PASS 2002 (Kaysville, UT).

The power to detect genetic associations with a binary trait depends on the frequency of the risk allele/genotype and the size of per-allele odds ratio of the genetic effect. To approximate power by the exemplary method to detect additive effects of alleles, we use a sample size of 2800 patients, anticipating that 60% will have CRA, and consider a range of MAFs, with p-value < 5x10-8 to claim genome-wide significance. We have 80% power to detect a SNP with a per-allele OR >1.5 for MAF of 0.2, or OR=1.7 for MAF=0.1, or OR=2.0 for MAF=0.05. These are consistent with effect sizes found in

other GWAS evaluations of toxicities. We will validate these findings in separate cohorts of patients as well.

With 2900 total pre-chemotherapy AMH levels in women with follow-up menstrual data, and using p-value < 0.05, we will have 80% power to detect a minimum OR of 1.11, where the OR represents the change in risk of CRA according to one standard deviation change in the pre-chemotherapy AMH. Another way to view this is that we will have 80% power to detect a difference in the mean AMH between patients with versus without CRA when the difference in means is at least 0.11 standard deviations of the pre-chemotherapy AMH. Because we expect only 2700 women (from this trial and others with both pre-chemotherapy and 1-year follow-up AMH levels, and using p-value < .05, we will have 80% power to detect a minimum OR of 1.12, where the OR represents the change in risk of CRA according to one standard deviation change in the difference between AMH at one year and AMH pre-chemotherapy. Another way to view this is that we will have 80% power to detect a difference in the mean AMH change between patients with versus without CRA, where the difference in means is at least 0.12 standard deviations of change in AMH.

17.10 Issues relating to racial and ethnic differences

Possible racial and ethnic variation in response to the treatment under consideration is of great concern to African-Americans. Researchers have noted poorer survival rates for African-American breast cancer patients as compared to Caucasians.[116,117] This difference has been attributed to many factors, including more advanced disease at the time of diagnosis,[118] social and economic factors,[119] or specific tumor characteristics such as ER positivity.[120,121] Although outcomes tend to be less favorable for African-Americans, significant race-by-treatment interactions have not been previously reported suggesting that, where treatment efficacy exists, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions.[122,123]

Potential for the enrollment of minority patients in this protocol is enhanced by the NRG Oncology's recognition of the importance of increasing minority accrual. To this end, we provide educational opportunities for NRG Oncology investigators and coordinators to increase their awareness and skills related to recruitment of racial and ethnic minority populations. The distributions of ethnicity and race for B-47 are projected from the NSABP B-28 study. The ethnicity distribution of the NSABP B-28 population consisted of 3% Hispanic and 97% non-Hispanic. The racial distribution in the B-28 study was 86% white; 8% black, not of Hispanic origin; 4% Asian or Pacific Islander descent; and 2% American Indian or Alaskan Native. The prognostic effect of race/ethnicity will be evaluated using statistical models. Unfortunately, because of power limitations, we will not be able to compare effects separately for the different cultural or racial groups.

TABLE 34. Expected racial and ethnic composition of NSABP B-47

Ethnic Category	Total
Hispanic or Latino	98
Not Hispanic or Latino	3,162
Ethnic Category: Total of all subjects	**3,260**
Racial Category	
American Indian or Alaskan Native	65
Asian	98
Black or African American	261
Native Hawaiian or other Pacific Islander	32
White	2804
Racial Category: Total of all subjects	**3,260**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American – a person having origins in any of the black racial Groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

18.0 PUBLICATION INFORMATION AND ADMINISTRATIVE AGREEMENTS

The trastuzumab supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

- Trastuzumab may not be used for any purpose outside the scope of this protocol, nor can trastuzumab be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for trastuzumab are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational trastuzumab contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

- For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):
  - NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
  - Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
  - Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
- Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

- When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

- Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

- Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

  E-mail: mailto:ncicteppubs@mail.nih.gov

  The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

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APPENDIX A
ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care; but unable to carry out any work activities.	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

2.0 ACTIVITIES OF DAILY LIVING

The following definitions for activities of daily living (ADL) should be used when the CTCAE v4.0 grading criteria are based on ADL:

- *Instrumental ADL* refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- *Self-care ADL* refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX B
HYPERTENSION MANAGEMENT RECOMMENDATIONS

1.0 SUGGESTIONS FOR ACCURATE BP ASSESSMENT

- Caffeine, exercise, and smoking should be avoided for at least 30 minutes before BP measurement.
- Patients should be seated for at least 5 minutes in a chair (rather than on an examination table), with feet on the floor, and arm supported at heart level.
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy.
- Palpated radial pulse obliteration pressure should be used to estimate systolic and diastolic BP.
  - The cuff should be inflated 20 to 30 mmHg above the level for the auscultatory determinations.
  - The cuff deflation rate for auscultatory readings should be 2 mmHg per second.
- Systolic BP is the point at which the first of 2 or more Korotkoff sounds is heard, and the disappearance of Korotkoff sound is used to define diastolic BP.

2.0 MANAGEMENT OF HYPERTENSION

The information provided in Table B1 was adapted from the JNC7 Report. For the complete article refer to:

Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: **The JNC 7 Report**. JAMA 2003; 289(19):2560-2572.

TABLE B1. Classification and management of blood pressure for adults aged 18 years or older

Blood Pressure Criteria				**Blood Pressure Management***	
BP Classification	**Systolic BP (mm Hg)***		**Diastolic BP (mmHg)***	**Lifestyle Modification**	**Initial Drug Therapy**
Pre-hypertension	120-139	*or*	80-89	Yes	No antihypertensive drug indicated
Stage 1 Hypertension	140-159	*or*	90-99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination
Stage 2 Hypertension	≥ 160	*or*	≥ 100	Yes	2-Drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)§

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

* Treatment determined by highest BP category.

§ Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

APPENDIX C
DETERMINATION OF MENOPAUSAL STATUS

The following criteria will be used in B-47 to define ***postmenopausal:***

- Age 56 or older with no spontaneous menses for at least 12 months prior to study entry; **or**

- Age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) **and** with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard; **or**

- Documented bilateral oophorectomy.

Women failing to meet one of these criteria will be classified as ***pre-menopausal***.

APPENDIX D
CTCAE GRADE 2 CARDIAC DISORDER ADVERSE EVENTS THAT PROHIBIT TRASTUZUMAB THERAPY

Trastuzumab will not be continued (Groups 2A and 2B) following any **grade 2** cardiac AE listed in the table below. (Trastuzumab should be administered following any of the other grade 2 AEs listed in the Cardiac Disorders section of the CTCAE v4.0 but not listed in this appendix or in Section 11.3.)

Note: See Sections 11.3 and 11.4 for trastuzumab therapy following ≥ grade 3 cardiac AEs listed in the Cardiac Disorders section of the CTCAE v4.0.

CARDIAC DISORDERS – CTCAE v4.0	
Adverse Event	**Grade 2 Criteria**
Acute coronary syndrome	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable
Atrioventricular block complete	Non-urgent intervention indicated
Chest pain - cardiac	Moderate pain; limiting instrumental ADL
Heart failure	Symptoms with mild to moderate activity or exertion
Mobitz (type) II atrioventricular block	Symptomatic; medical intervention indicated
Mobitz type I	Symptomatic; medical intervention indicated
Myocardial infarction	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes
Myocarditis	Symptoms with mild to moderate activity or exertion
Pericarditis	Symptomatic pericarditis (e.g., chest pain)
Right ventricular dysfunction	Symptoms with mild to moderate activity or exertion
Sick sinus syndrome	Non-urgent intervention indicated
Sinus bradycardia	Symptomatic, medical intervention indicated
Ventricular arrhythmia	Non-urgent medical intervention indicated
Ventricular tachycardia	Non-urgent medical intervention indicated

APPENDIX E
TRASTUZUMAB INFORMATION AND INSTRUCTIONS FOR ALL IRELAND CO-OPERATIVE ONCOLOGY RESEARCH GROUP (ICORG)

The NCI will not supply trastuzumab to ICORG for the B-47 study. ICORG investigators must follow Appendix E trastuzumab drug supply information and instructions. Refer to Protocol Section 12.2.9 for trastuzumab warnings and contraindications; also refer to Sections 13.1 and 13.2 for information regarding expectedness of adverse events (including the trastuzumab CAEPR list). For additional information about possible side effects, refer to the current Investigator's Brochure for trastuzumab (see Protocol Section 12.2).

1.0 DESCRIPTION OF TRASTUZUMAB (HERCEPTIN®)

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd=5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each trastuzumab vial contains 150 mg trastuzumab, α,α-trehalose dihydrate, L-histidine HCl, L-histidine, and polysorbate 20.

2.0 PROCUREMENT OF TRASTUZUMAB

Trastuzumab will be supplied free-of-charge to ICORG investigators by F. Hoffmann-La Roche, Ltd. and distributed by the Roche Distribution Network. A starter shipment of trastuzumab will be dispatched directly to the investigator following study initiation by ICORG at the site. Thereafter, investigators will request trastuzumab by utilizing their usual ICORG-specific procedures for requesting study drug supply. Trastuzumab will be shipped directly to the address of the treating investigator on file with NRG Oncology.

3.0 SHIPPING

Vials of trastuzumab are shipped with qualified, time controlled shippers ***Monday through Wednesday***, and must be placed in a 2°–8°C (36°–46°F) refrigerator immediately upon receipt to ensure optimal retention of physical and biochemical integrity.

4.0 STORAGE/STABILITY

Vials of trastuzumab are stable at 2°–8°C (36°–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. After reconstitution with SWFI (not supplied), the reconstituted solution should be used immediately. Any remaining reconstituted solution should be discarded. Do not freeze trastuzumab that has been reconstituted.

Solutions of trastuzumab for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 0.9% solution for injection for 24 hours at temperatures not exceeding 25°C.

From a microbiological point of view, the reconstituted solution and trastuzumab infusion solution should be used immediately. The product is not intended to be stored after reconstitution and dilution unless this has taken placed under controlled and validated aseptic conditions.

5.0 RECONSTITUTION AND ADMINISTRATION (TRASTUZUMAB 150 MG POWDER)

5.1 Reconstitution

Each vial of trastuzumab (150 mg) is reconstituted with 7.2 mL of SWFI (not supplied). Use of other reconstitution solvents should be avoided. This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab.

Shaking the reconstituted trastuzumab or causing excessive foaming during the addition of diluent may result in problems with dissolution and the amount of trastuzumab that can be withdrawn from the vial. Use appropriate aseptic technique when performing the following reconstitution steps:

- Trastuzumab should be carefully handled during reconstitution. Using a sterile syringe, slowly inject 7.2 mL of SWFI into the vial containing the lyophilized cake of trastuzumab. The stream of SWFI should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. ***DO NOT SHAKE.***
- Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted trastuzumab results in a colorless to pale yellow transparent solution and should be essentially free of visible particulates.
- The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared, it should be administered immediately. If diluted aseptically, it may be stored for 24 hours (do not store above 25°C).

5.2 Administration

See Protocol Sections 9.2 (Group 2A patients) or 9.4 (Group 2B patients).

6.0 DRUG TRANSFER

ICORG policy does not permit the transfer of trastuzumab outside the scope of this protocol, nor can trastuzumab be transferred or licensed to any party not participating in this clinical study.

7.0 DRUG RETURN/DESTRUCTION

Unused or expired drug will be destroyed in the Pharmacy service of each center as per each center's policy and guidelines, or returned to the vendor in cases where it is not possible for the site to destroy the drug locally.

8.0 DRUG ACCOUNTABILITY

The investigator, or a responsible party designated by the investigator, must maintain a careful record of receipt, disposition, and return of the trastuzumab received through the B-47 study. ICORG sites must use ICORG drug accountability logs provided. These logs include the dates the study medications are received from the manufacturer, the dates dispensed for the individual patient, and the dates destroyed at the site per institutional policy and guidelines (or returned to manufacturer/supplier if authorized). Patient number, date of infusion, investigator name, batch or lot numbers, expiry date, quantity, pack number (if applicable) of the study medication must be documented on the logs. Drug accountability logs will be provided to sites in the study files at the time of study initiation.